American Heart Journal

An international publication for the study of the circulation

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VOLUME 62

JULY-DECEMBER, 1961

VOLUME 62

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Printed in the United States of America

American Heart Journal

July, 1961, Volume 62, Number 1

Editorial

Reflections on the nature of renal tubular reabsorption

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For many years, particularly at the beginning of this century, renal physiologists were preoccupied with the question of how, and how much, glomerular fluid is formed. It is now more or less universally agreed that in man, over a 24-hour period, roughly 180 liters are formed by the process of ultrafiltration. Since in the usual course of events about 1 liter of urine is formed daily, workers in the field of renal physiology are presently concerned with the nature of the forces which contrive to return 179 liters of fluid to the peritubular capillaries each day.

The earliest suggestion in this regard was offered by Carl Ludwig,[1] who was the first to appreciate the fact that the volume of urine represented but a small fraction of the total turnover of fluid in the kidney. In his eyes, this organ represented a modified capillary bed with anatomically discrete filtrative and reabsorptive areas separated from one another by the tubular wall. The tubular membrane was thought to have permeability characteristics which differed only slightly from those of the glomerular membrane. This would permit most of the tubular fluid to be drawn freely into the adjacent capillaries in answer to the same oncotic forces which serve to reabsorb filtered fluid in the capillary beds of the body at large. Thus, urine was thought, by Ludwig, to be formed in a manner very similar to the way in which we conceive of the formation of lymph today.

Since the cells which line most of the tubular wall resemble those in secreting organs, Ludwig's views met with considerable opposition. In closer adherence to Bowman's original suggestions, it was widely believed that most urinary solids were deposited into the tubular lumen by cellular secretion, with small amounts of glomerular fluid, not in excess of the final volume of urine, being formed to wash these down.

Some 40 years ago, Arthur Cushny summarized much of the existing evidence and described the "modern theory of the urinary secretion."[2] In this view, large volumes of fluid are formed by ultrafiltration at the glomerulus, followed by the reabsorption of almost equally large volumes at the tubular level, as originally suggested by Ludwig. However, Cushny's interpretation of the process of tubular reabsorption differed sharply. Since Ludwig's simple concept of an inert tubular membrane could only account for the formation of

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Received for publication Jan. 6, 1961.

urine isosmotic to plasma, and could not account for observed differences in composition between urine and plasma, Cushny ascribed reabsorption to a vital activity of tubular cells. The tubular cell was conceived of as a sort of pump which deposited an ideal Locke's solution into the peritubular surround.

In 1948, Wesson, Anslow and Smith[3] took exception to this nebulous description of the tubular activity and offered in its place a more precise formulation. They agreed with Cushny that most filtered solutes are not free to diffuse across the tubular wall; but differed from him by suggesting individual transport systems for each of the impermeant solutes returned to the surrounding capillaries. In the proximal tubule, where the bulk of reabsorption takes place, they postulated a water-permeable but sodium-impermeable membrane barrier. The force accounting for the movement of large volumes of fluid was described as arising from active transport of sodium, with water following passively to achieve osmotic equilibration. They obtained data on the excretion of sodium and water during strong mannitol diuresis, which, when interpreted in the light of certain critical assumptions, lent support to their thesis.

That active transport of sodium occurs in some tubular area is implicit in the formation of a urine with a sodium content lower than that of plasma. The micropuncture studies of Richards and associates[4] in the amphibian, and of Walker and associates[5] in the mammalian kidney demonstrated that sodium moves against a concentration gradient in some distal regions of the tubule. It is reasonable, therefore, to suppose that a similar active transport mechanism would be required to move sodium across the proximal tubular wall. The fact that micropuncture studies, under more or less physiologic conditions, have not generally shown a significant sodium-concentration gradient between proximal tubular fluid and plasma is readily explained by postulating a high permeability to water of the tubular wall in this area. More recently, micropuncture studies during mannitol diuresis have revealed lower concentrations of sodium in proximal tubular fluid than in plasma.[6] This indicates active transport of sodium in the proximal tubule, at least under conditions of osmotic diuresis. These studies, as well as others, have reinforced the original interpretations of Homer Smith and his collaborators which have served as the framework for much of the thinking in renal physiology during the past decade.

However, certain logical consequences of the construction of tubular activity outlined above lead to difficulties which require close examination. Separate tubular transport systems are required for each molecular and ionic species filtered at the glomerulus and destined to return to the blood stream, but not free to diffuse across the tubular wall. When viewed in aggregate these transport systems constitute an outwardly directed cellular secretory activity of considerable dimensions. In man, 179 liters of secreted fluid must be deposited daily in the peritubular area. Though the polarity has been reversed, the role of secretion in the ultimate formation of urine is no less important than that ascribed to it by the Bowman-Heidenhain school of the latter half of the nineteenth century. It has, however, assumed quantitative proportions that probably would have dismayed even the vitalists of that era. However, since the capacity, per gram of tissue, of the salt-secreting glands of certain marine avian species is in this order of magnitude,[7] there are no a priori grounds for supposing that the tubules of the kidney would not be equal to this task.

There are nonetheless greater conceptual difficulties posed by current theory relating to tubular reabsorption. In the ordinary course of events the daily urinary output of salt and water is a very small remainder of two large opposing processes. A small percentile variation in either the amount of sodium filtered, without concomitant change in the amount reabsorbed, or vice versa, could lead to large fluctuations in the urinary output, well beyond the changes ordinarily observed. It is clear, therefore, that the rate at which sodium is filtered and the rate at which it is reabsorbed remain in remarkably close balance with one another. No satisfactory explanation of how two processes of such dissimilar nature can continue to operate at essentially the same rate has yet been ad-

vanced.* The quantity of glomerular fluid formed is related to physical parameters, such as hydrostatic and oncotic pressures. Active tubular transport of sodium is regarded to be a chemical process governed by metabolic conditions prevailing in the cell.

One might perhaps imagine that nature has neatly contrived an anatomic balance between the filtering surface and the tubular secretory mass, with each of these relatively fixed and capable of only slight variation. This supposition is contradicted by the fact that they may vary widely, although almost invariably in close companionship with one another. This is clearly demonstrated in the experiment of Lottspeich and associates,[10] in which the rate of filtration was acutely elevated by the administration of amino acid. Although the filtration rate was nearly doubled, each increment in the filtered load of chloride was accompanied by proportional and almost equal changes in the tubular reabsorption of chloride. Although sodium was not measured in these experiments, the same behavior for this ion can be presumed without question. This clearly demonstrates that it is covariance rather than invariance which accounts for glomerulotubular balance.

It is conceivable that this covariance could result from the opening of inactive nephrons. However, such intermittent activity is not thought to occur in the mammalian kidney.[11] We must suppose, therefore, that the rate of transport of sodium in individual tubules rises and falls with fluctuations in the rate of filtration. How could such a remarkable synchronization occur? Are we to imagine that the renal tubular cell is possessed with the mysterious propensity for sensing the rate of filtration of sodium upstream to it, and for promptly and accurately adjusting its pumping rate to match? The conceptual difficulty posed here applies not only to sodium, but also to other ions which are largely but not completely reabsorbed. These considerations suggest that current theory in regard to the nature of tubular reabsorption of strong electrolytes may require revision.

What is required is a model of the kidney which might explain, or at least offer reasonable hope of explaining, the close companionship of the volumes of fluid constantly filtered and reabsorbed. A well-known example of such a system has been defined for us in the capillary beds of the body at large, where approximately equal yet large volumes of fluid undergo filtration and reabsorption. This leads us back to Ludwig's concept of the kidney as described earlier, wherein the turnover of fluid in the kidney arises from the operation of the same forces which operate in capillary beds elsewhere. It will be recalled that Cushny rejected Ludwig's concepts relative to tubular reabsorption because the urine formed would always be isosmotic to plasma and plasma-like in composition. Subsequent studies,[5] which of course were not known to Cushny at the time he was formulating his theory, have revealed that the bulk of reabsorption takes place in the proximal tubule, and that the fluid emerging is isosmotic to plasma and plasma-like in its strong electrolyte composition. Therefore, it now seems reasonable to suppose that the predominant mechanism leading to reabsorption may be one not very different from that originally conceived by Ludwig. This would place at our disposal an alternative model of the renal function wherein both filtration and, to a large extent, tubular reabsorption are governed by a common set of physical parameters. The proximal tubular membrane is here assumed to be essentially freely permeable to electrolytes, so that oncotic and hydrostatic forces, similar to those at play in other capillary beds, are free to contribute importantly to the filtration-reabsorption steady state. However, since the permeability characteristics of the glomerular and tubular membranes differ with respect to certain solutes, such as urea, and because some solutes, such as glucose, are actively transported, the conditions leading to a steady state are considerably more complex than those in other capillary beds. All other factors being constant, the degree to which glomerular fluid is re-

*It has been suggested that if the resistance to hydrodynamic flow across the glomerular membrane were less than that down the course of the tubule, the rate of active transport of sodium could influence the rate of glomerular filtration.[8,9] However, it seems altogether unlikely that resistance to flow through a membrane, the pores of which are measured in Angström units, would be less than through a tubule, the lumen of which is measured in micra.

absorbed will depend on the relative osmotic activity of impermeant solutes within the tubule as compared to that of the impermeant solutes in the peritubular surround.[12] The osmotic activity of the latter will be governed by a number of factors, such as the concentration of protein in the plasma of the peritubular capillaries, the rate of deposition of osmotically active solutes, such as glucose, into the peritubular surround, and the rate of plasma washout of these as determined by plasma flow.

The crucial point of difference between what may be termed the physical and secretory approaches to the problem of tubular reabsorption resides in the assumed permeability characteristics of the proximal tubular membrane with respect to strong electrolytes. In the absence of sufficient direct evidence, at least with respect to the mammalian kidney, there has been a natural reluctance to concede that a cellular barrier such as that posed by the tubular wall would permit essentially free diffusion of electrolytes across it.[13] However, in the case of the upper intestinal tract, Ussing[14] has pointed out that the permeability of the mucosal wall with respect to sodium is so great that physical forces predominate over active transport. There would seem to be no a priori reason why a similar predominance of passive diffusion over active transport should not prevail for the proximal tubular wall.

In an attempt to gain insight into the problem of whether the proximal tubular wall acts mainly as a pump for sodium or permits free diffusion of this ion, we compared the rate of tubular reabsorption of sodium at high and normal levels of plasma salt.[15] It was reasoned that, if the membrane permitted essentially free diffusion, the formation of a hypernatric filtrate would obligate the reabsorption of a hypernatric reabsorbate. Thus, paradoxically, more sodium would be reabsorbed by the animal while hypernatremic than at normal levels of plasma salt. On the other hand, if the tubular wall functioned as an active transport system, responsive to body needs, the rate of tubular reabsorption should decrease, or at least remain unchanged, when levels of plasma salt are elevated. The data revealed that although the dogs filtered and excreted more sodium when hypernatremic, as would be expected, they also *reabsorbed* more sodium. Moreover, the increments in sodium reabsorption were proportional to the increments in levels of plasma sodium. This finding, that tubular reabsorption of sodium is increased in the face of hypernatremia and total body surfeit of salt, favors the operation of an indiscriminate process such as diffusion as the predominant mechanism. When we attempt to interpret these data in the light of the current concept of tubular reabsorption, we are forced to suppose that one or more of the active systems for sodium transport are stimulated to conserve sodium at a time when the dictates of body economy demand excretion.*

There are other observations which are well explained with the modified Ludwigian model of the kidney but require strained interpretation when examined in the light of present-day concepts. For example, it has been postulated[16] that potassium is actively reabsorbed in the proximal tubule, only to be secreted by an oppositely directed transport process, into the tubule at a more distal locus. Since it has been shown that the concentrations of potassium and sodium remain plasma-like in proximal tubular fluid,[5,17] it would appear much simpler to suppose that, in this area of the tubule, they are both reabsorbed as a result of being passively included in the filtration-reabsorption stream. If they were each reabsorbed by individual transport systems, these would have to somehow pump at continuously synchronous rates.

An important problem facing renal physiologists is how the kidney operates to maintain a constant extracellular fluid volume. The kidneys of bilaterally adrenalectomized animals, maintained in good condition by fixed hormonal replacement, regulate volume normally.[18] The transplanted denervated kidney retains the ca-

*In these experiments the elevation of sodium concentration is essentially the same on both sides of the tubular cell. Therefore, one cannot imagine that a unidirectional transport process is stimulated by a favorable substrate gradient. Moreover, in the experiments cited earlier,[10] tubular reabsorption of chloride kept pace with changing filtered loads, with no change in the concentration of ultrafiltrate. The operation of an indiscriminate transport mechanism, such as that for glucose, is ruled out by the fact that salt escapes reabsorption at low as well as at high filtered loads.

pacity to regulate volume normally.[19] It is clear, therefore, that the kidney is capable of regulating the volume of extracellular fluid without regard to a control exerted by the level of any of the adrenal hormones, in the circulating blood, and without regard to a direct neural control. Aside from the possibility that some unidentified hormone exerts a control over tubular activity, it would appear that renal hemodynamic changes may be responsible for the changes in urinary output observed after contraction or expansion of extracellular volume.

During states of circulatory insufficiency as a result of contraction of plasma volume[20] or heart failure,[21] renal plasma flow falls to very low values. The rate of glomerular filtration may remain normal or is usually reduced to a lesser extent.* Under such conditions, presumably because of an increase in intraglomerular pressure, more fluid is filtered from each unit volume of plasma flowing through the glomerulus. The plasma leaving the glomerulus to perfuse the peritubular capillaries would, therefore, have a higher content of protein. Using the modified Ludwigian model of the kidney, I[22] and others[23,24] have suggested that this increased oncotic activity in the peritubular capillaries could lead to an increased absorption of tubular fluid, thus accounting for the oliguria observed. Other aspects of the altered hemodynamic pattern, such as the reduced rate of plasma washout of osmotically active particles from the peritubular surround, may play equally or perhaps even more important roles in determining the extent of tubular reabsorption. So little is known about possible changes in the distribution of blood flow and pressure relationships in the kidney during circulatory insufficiency that these can only be speculated upon at present.

In summary, the current theory regarding the reabsorption of strong electrolytes postulates the careful metering out, by the tubular cells, of huge but exact proportions of ions in order to form a reabsorbate practically identical to ultrafiltrate in composition. It has been pointed out that, if sodium and potassium were largely or exclusively pumped across the proximal tubular wall, it would be necessary to attribute a number of highly unusual characteristics to the transport systems involved. These are: (1) the ability to sense alterations in the rate of filtration and adjust their pumping rates to match; (2) the anomalous characteristic of returning more sodium to the body under certain conditions when the need for excreting salt is great; (3) the ability to synchronize the rates of transport of sodium and potassium so as to maintain a constant and plasma-like ratio of these ions in proximal tubular fluid.

Since the electrolyte composition and volume of reabsorbate is very similar to that of ultrafiltrate, an alternative model of the renal function is proposed, in which the large volumes of fluid reabsorbed in the proximal tubules return across an essentially electrolyte-permeable wall in answer to forces similar to, but not identical with, those existing in other capillary beds. The major modifications in the electrolyte composition of urine would be accomplished by active transport systems located in more distal tubular regions. Thus, with respect to water and electrolytes, excepting perhaps bicarbonate, the main function of the proximal tubule would be to reduce the volume of ultrafiltrate, whereas the main function of the distal tubular segments would be to alter the electrolyte composition of the fluid finally emerging as urine.

*If circulatory insufficiency is extreme, the flow to and pressure in many glomeruli may become so reduced that no filtrate is formed. Under such conditions of inhomogeneity, the overall filtration fraction may fall to normal or low values; yet the nephrons actively engaged in the formation of urine may have very high filtration fractions. This may explain why in severe shock, renal disease, or perhaps under certain other circumstances the presence or degree of oliguria does not necessarily correlate with the filtration fraction.

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Clinical communications

Calcium, chelates, and digitalis
A clinical study

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In 1921, Singer[1] aptly described calcium as "the whip and the rein of digitalis." It is recognized that calcium plays a prominent role in provoking and perpetuating cardiac arrhythmias. Calcium, as well as other metallic ions, mimics digitalis in many ways and is synergistic.[2] Therefore, if ionized calcium is decreased, digitalis effect might likewise be diminished.[3,4]

One of the most effective methods of producing a rapid, transient hypocalcemia is through the intravenous use of trisodium ethylenediamine tetraäcetate (Na_3EDTA). The term *chelating agent* is derived from the Greek *chelate* meaning claw. A chelate, then, is a chemical compound formed between a metallic ion and a molecule having two neighboring groups capable of simultaneously combining with a metal to form a ring structure. Na_3EDTA has a powerful and preferential affinity in the binding of calcium. It is the purpose of this paper to report our experience with 92 infusions of Na_3EDTA in 66 patients.

Types of patients and procedure employed

A total of 66 patients received 92 intravenous infusions of Na_3EDTA. Forty-five males and 21 females were studied. Their ages ranged from 9 months to 90 years. Thirty-five patients had unequivocal historical, clinical, and electrocardiographic evidence of a cardiac arrhythmia or conduction disturbance resulting from absolute overdosage of digitalis. Relative digitalis overdosage was not studied except when specifically mentioned. Sixteen patients also had cardiac arrhythmias but had not been on any digitalis preparation for at least 6 weeks. This latter group was composed mainly of patients with arteriosclerotic or rheumatic heart disease. Exceptions will be pointed out later in the text. Three digitalized patients with miscellaneous arrhythmias were also treated. Twelve patients had neither clinical nor electrocardiographic evidence of arrhythmia or cardiac disease. A second infusion was given in 26 patients. Since the results of the second infusion were invariably similar to those of the initial infusion, they will not be discussed separately.

Sixty-six patients received a total of 92 intravenous infusions of Na_3EDTA, averaging 3.25 Gm. in 12 minutes (1.25 to 4.0 Gm. in from 5 to 120 minutes). The solution was made up as a 15 mg. per cubic centimeter solution (4 Gm. of Na_3EDTA in 250 c.c. of 5 per cent glucose in water). The Na_3EDTA used was packaged as a 1.0 Gm. 5 c.c. aqueous solution.† The

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Received for publication Oct. 21, 1960.
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Table I. *First-degree heart block*

Patient number, age, sex	*Digitalis preparation*	*ECG before test: P-R (sec.)*	*EDTA infusion*		*ECG after test: P-R (sec.)*	*Effect observed*	
			Dose (Gm.)	*Time required (min.)*		*Onset (min.)*	*Duration*
1. H.J. 48, M	None	0.26	3.0	10	0.21	7	60 min.
2. M.H. 82, F	Digoxin	0.29	4.0	12	0.22	10	30 min.
3. A.H. 70, M	Digitalis leaf	0.28	3.5	15	0.21	5	6 hr.
4. L.S. 54, M	Digoxin	0.23	4.0	12	0.20	3	8 hr.
5. A.J. 62, M	Digitoxin	0.48	3.5	8	0.32	5	30 min.
Average		0.31	3.6	11.4	0.23	6	192 min.

*Patients 2, 3, 4, and 5 were taken off digitalis and given oral potassium. Within 10 days all had P-R intervals of less than

average infusion was 255 mg. per minute (range, 50 to 800 mg. per minute).

The electrocardiogram was monitored for 3 to 5 minutes prior to each infusion, and records were taken at 1-minute intervals or less during the infusion. The end point was the presence or absence of a change in the rhythm or conduction. Follow-up tracings were recorded after 24 hours in the majority of patients.

Where studied in 32 patients, the serum calcium ranged from 5.2 to 16.2 mEq./L. (average, 6.5 mEq./L.) prior to, and from 4.1 to 14.8 mEq./L. (average, 5.3 mEq./L.), after the infusion. Serum potassium ranged from 2.8 to 5.2 mEq./L. (average, 3.8 mEq./L.) and did not change. Sodium, carbon dioxide, blood urea nitrogen, and chloride were also unaffected. All samples of blood were drawn from the arm opposite the site of infusion. Studies on serum electrolytes were discontinued later because of the uniform finding of a hypocalcemic effect, and the doubtful relationship of this value to actual ionized calcium. Levels of serum phosphorus were not run. Blood pressure, pulse, respiratory rate, clinical signs of hypocalcemia, and subjective complaints of digitalis intoxication were observed before, during, and after all infusions.

Results

First-degree atrioventricular block. All 5 patients studied had an average shortening of 0.08 second of the P-R interval, and the depression of the S-T segment was lessened (Table I). The heart rate decreased 25 per cent in 4 patients, and was 10 per cent increased in Patient 1.

COMMENT. All patients were digitalized and had evidence of absolute overdosage except Patient 1, who had proved primary hyperparathyroidism. It is of interest that the response in this patient was similar to that in those who were overdigitalized. First-degree atrioventricular block disappeared permanently in the overdigitalized patients when digitalis was withdrawn and administration of oral potassium chloride was instituted. We assume, therefore, that the prolonged P-R interval was due to digitalis overdosage.

Serum calcium (mEq./L.)		*Serum potassium (mEq./L.)*		*Subjective symptoms*		*Remarks*
Before	*After*	*Before*	*After*	*Before*	*After*	
16.2	14.8	3.8	3.6	0	0	Primary hyperparathyroidism
5.2	4.8	4.0	4.1	0	0	*
6.4	5.0	3.6	3.8	++	0	*Nausea remitted permanently. Arm pain above infusion site.
5.8	4.4	3.1	3.3	+++	0	*Nausea remitted permanently. Arm pain above infusion site
—	—	—	—	0	0	*Arm pain above infusion site
8.4	7.4	3.6	3.7			

0.20 second and no subjective complaints. Before: Before infusion. After: Immediately after infusion.

Second-degree atrioventricular block. Five patients with absolute digitalis overdosage had second-degree atrioventricular block. Four of the 5 patients reverted to sinus rhythm with first-degree block, and one of these (Patient 6) developed a normal P-R interval (Table II). With the exception of elimination of premature ventricular contractions, the ECG of the other patient was unchanged (Patient 9), although his rhythm later reverted to normal sinus rhythm when oral potassium was administered and digitalis withdrawn. The electrocardiograms of all patients in this group maintained the Na_3EDTA effect when digitalis was removed and oral potassium chloride was given.

Patient M. W. deserves special mention. This 9-month-old Negro boy, who weighed 8.5 kilograms, had many congenital anomalies, including involvement of the renal and cardiovascular system. He had developed congestive failure and had been on maintenance digoxin for several weeks. The child, through error, had received 0.6 mg. of digoxin (10 times his maintenance dose). Two hours and 20 minutes later, profuse vomiting and diarrhea developed, the blood pressure fell, and the child's condition appeared to be terminal. The ECG revealed second-degree A-V block. Infusion of Na_3EDTA was administered, and 10 minutes thereafter his blood pressure returned to normal, vomiting ceased, and he took and retained oral fluids. Twenty minutes later, and after he had received 1.0 Gm. of Na_3EDTA, the ECG reverted to sinus rhythm with a first-degree A-V block (Fig. 2). The rhythm returned to second-degree A-V block on several occasions but could be restored to first-degree block merely by speeding up the rate of infusion. However, tetany developed 30 minutes after the start of the infusion and after 1.2 Gm. of Na_3EDTA had been given. At this time, the ECG showed sinus arrest with a slow nodal rhythm. Two cubic centimeters of 10 per cent calcium gluconate were given intravenously, and irreversible ventricular fibrillation, shock, and death ensued almost immediately. Intravenous potassium chloride was ineffectual.

Table II. *Second-degree A-V block in patients with digitalis intoxication*

Patient number, age, sex	*Digitalis preparation*	*ECG before test*	*EDTA infusion*		*ECG after test**	*Effect observed*		*Serum calcium (mEq./L.)*		*Serum potassium (mEq./L.)*		*Subjective symptoms*		*Remarks*
			Dose (Gm.)	*Time required (min.)*		*Onset (min.)*	*Duration*	*B*	*A*	*B*	*A*	*B*	*A*	
6. M.W. 74, F	Digitoxin	Type II 2:1 A-V block	3.0	19	Sinus rhythm, P-R 0.20 sec.	8	Permanent	6.4	5.1	5.1	5.2	++++	0	Nausea and visual disturbance remitted during infusion
7. J.M. 72, M	Digitalis leaf	P.A.T. with 2:1 A-V block	2.5	10	First-degree block, P-R 0.33 sec.	10	35 min.	—	—	—	—	—	—	Arm pain above infusion site
8. L.K. 60, M	Gitalin	Type I second-degree A-V block, Wenckebach phenomenon	4.0	9	First-degree block, P-R 0.22 sec.	10	Permanent	6.2	4.9	3.4	3.6	—	—	———
9. R.T. 71, M	Digitoxin	Type I second-degree A-V block, Wenckebach and 12 PVCs/min.	4.0	7	Second-degree A-V block. No PVC	6	Permanent	5.9	4.7	3.7	3.9	+++	0	Nausea remitted during infusion
10. M.W. 9 mo., M	Digoxin	Second-degree A-V block	1.2	10	Sinus rhythm, First-degree A-V block, P-R 0.21 sec.	10	Permanent	—	—	—	—	+++	0	Developed tetany and died in ventricular tachycardia when I.V. calcium was given. Child had many severe congenital anomalies. Vomiting ceased
Average			2.9	11		8.8	Permanent	6.2	4.9	4.1	4.2			

*All of the electrocardiograms returned to normal within 14 days after administration of oral potassium chloride and temporary withdrawal of digitalis.
B: Before infusion. A: Immediately after infusion. P.A.T.: Paroxysmal atrial tachycardia. PVC: Premature ventricular contractions.

Table III. *Complete A-V block in patients believed to be digitalis intoxicated*

Patient number, age, sex	*Digitalis preparation*	*ECG before test*	*EDTA infusion*		*ECG after test*	*Effect observed*		*Serum calcium (mEq./L.)*		*Serum potassium (mEq./L.)*		*Subjective symptoms*		*Remarks*
			Dose (Gm.)	*Time required (min.)*		*Onset (min.)*	*Duration*	*B*	*A*	*B*	*A*	*B*	*A*	
11. A.H. 70, M	Digitoxin	Complete A-V block. Rates:atrial 88, ventricular 40	3.0	15	First-degree A-V block, P-R 0.23 sec.	10	Permanent	6.2	4.9	3.6	3.6	++	—	Nausea remitted. Arm pain above infusion site
12. L.R. 72, F	Leaf	Complete A-V block. Atrial fibrillation with ventricular rate of 36	3.5	20	No change	10	30 min.	6.5	5.1	3.1	3.3	—	—	Died
13. R.P. 64, M	Leaf	Complete A-V block. Rates:atrial 65, ventricular 38	3.0	9	Sinus rhythm, P-R 0.20 sec.	5	Permanent	—	—	—	—	++	—	Nausea remitted. Arm pain above infusion site
14. R.W. 74, M	Digoxin	Complete A-V block. Rates:atrial 68, ventricular 40	4.0	22	First-degree A-V block, P-R 0.24 sec.	10	Permanent	—	—	—	—	—	—	———
15. A.B. 60, M	Digitoxin	Complete A-V block. Rates:atrial 50, ventricular 40	3.5	30	Rate 68 per minute, P-R 0.16 sec.	11	60 min.	—	—	—	—	—	—	———
16. B.H. 74, F	Digoxin	Rates:atrial 72, ventricular 36	4.0	10	First-degree A-V block, P-R 0.33 sec.	5	20 min.	5.6	4.4	3.9	4.1			Arm pain above infusion site
17. M.L. 60, M	Digitoxin	Rates:atrial 85, ventricular 35	2.0	20	Complete block, atrial 85, ventricular 42	—	—	—	—	—	—	—	—	Low dosage with slow administration. Reverted to sinus rhythm on KCl and removal of digitalis
Average			3.28	18		8.5	—	6.1	4.8	3.5	3.7			

B: Before infusion. A: Immediately after infusion.

Table IV. *A-V dissociation believed to have resulted from digitalis intoxication*

Patient number, age, sex	*Digitalis preparation*	*ECG before test*	*EDTA infusion*		*ECG after test*
			Dose (Gm.)	*Time required (min.)*	
22. B.H. 60, F	Digitoxin	A-V dissociation	3.0	30	Sinus rhythm
23. E.S. 48, F	Digoxin	A-V dissociation	2.0	15	First-degree A-V block, P-R 0.24 sec.
24. B.T. 80, F	Digitoxin	A-V dissociation	3.0	10	Sinus rhythm
25. G.S. 65, F	Digoxin	A-V dissociation	3.5	10	Sinus rhythm
26. R.N. 61, M	Digoxin	A-V dissociation	4.0	12	Sinus rhythm
Average			3.1	13.4	

Table V. *Summary of 12 patients with atrial fibrillation, 7 of whom were digitalized*

Patient number	*Digitalis preparation*	*ECG before test*	*EDTA infusion*		*ECG after test*
			Dose (Gm.)	*Time required (min.)*	
24–33.	3 Digitoxin 3 Digoxin 1 Digitalis	Atrial fibrillation	3–4	10–20	Atrial fibrillation, 26 per cent increase in ventricular rate. Range, 15-35 per cent
34–38.	None	Atrial fibrillation	3–4	10–20	Atrial fibrillation, 12 per cent increase in ventricular rate. Range, 10-15 per cent

COMMENT. This patient's course suggests the following: (1) Na_3EDTA was able to reverse the cardiac arrhythmia secondary to considerable absolute digitalis overdosage. (2) There was a narrow margin between tetany and therapeutic effect in this child. (3) There is profound danger in the use of intravenous calcium in digitalized patients, even when Na_3EDTA is present. Death rarely results from tetany, and, thus, intravenous calcium should probably be withheld, if at all possible. The danger of ventricular fibrillation is greater than that of tetany. (4) The dramatic cessation of gastrointestinal symptoms pursuant to Na_3EDTA was striking and is perhaps an

Effect observed		*Serum calcium (mEq./L.)*		*Serum potassium (mEq./L.)*		*Subjective symptoms*		*Remarks*
Onset (min.)	*Duration*	*Before infusion*	*After infusion*	*Before infusion*	*After infusion*	*Before infusion*	*After infusion*	
25	24 hr.	6.4	4.8	3.4	3.3	—	—	Arm pain above infusion site
7	Permanent	—	—	—	—	—	—	———
8	Permanent	5.4	4.1	3.5	3.5	—	—	Arm pain above infusion site
6	12 hr.	7.1	5.8	3.6	3.7	++	—	Arm pain above infusion site. Nausea remitted
8	12 hr.	7.0	5.6	3.7	3.9	++	—	Nausea remitted
7.7	—	6.4	5.1	3.6	3.6			

Effect observed		*Serum calcium (mEq./L.)*		*Serum potassium (mEq./L.)*		*Subjective symptoms*		*Remarks*
Onset (min.)	*Duration (hr.)*	*Before infusion*	*After infusion*	*Before infusion*	*After infusion*	*Before infusion*	*After infusion*	
10	1–3	6.8	5.4	4.0	3.9	1/7	0/7	2 of the 7 patients had arm pain above the infusion site
10	1	6.2	5.1	3.9	3.9	0	0	3 of the 7 patients had arm pain above the infusion site

indication that the subjective complaints of digitalis intoxication are also relieved by the binding of ionized calcium.

Complete atrioventricular block. Ten patients with complete heart block were studied, and in 7 of these the block was believed to be the result of absolute digitalis overdosage. Sinus rhythm, or first-degree block, replaced the complete block in 5 of these 7 patients on digitalis (Fig. 3). Failure in one patient (Patient 17) was later converted when oral potassium was administered and digitalis was withdrawn (Table III). It should be noted that the amount of Na_3EDTA was small and slowly infused in this patient. Another patient in

Table VI. *Summary of findings in patients with premature ventricular contractions on digitalis*

Patient number, age, sex	*Digitalis preparation*	*ECG before test*	*EDTA infusion*		*ECG after test*
			Dose (Gm.)	*Time required (min.)*	
39. O.D. 63, F	Digoxin	Bigeminy with re-entry	3.0	12	First-degree A-V block, P-R 0.22 sec.
40. E.L. 58, F	Digitoxin	Bigeminy with re-entry	2.5	20	N.S.R.
41. R.T. 65, M	Digoxin	Trigeminy	3.5	7	N.S.R.
42. L.K. 70, M	Digitalis	Trigeminy	4.0	10	N.S.R.
43. H.B. 68, M	Digoxin	17 PVC/min. re-entry	3.5	10	N.S.R.
44. M.M. 62, M	Digoxin	12 PVC/min.	4.0	15	2 PVC/min.
45. J.T. 70, F	Digitoxin	17 PVC/min.	4.0	10	17 PVC/min.
46. R.J. 58, M	Digoxin	15 PVC/min.	3.5	20	14 PVC/min.
47. T.H. 70, F	—	Bigeminy with re-entry	4.0	10	No change
48. H.V. 60, M	—	Bigeminy with re-entry	4.0	10	No change
49. V.P. 45, M	—	18 PVC/min.	4.0	12	15 PVC/min.
50. G.S. 71, M	—	11 PVC/min.	4.0	12	6 PVC/min.
51. W.S. 64, M	—	7 PVC/min.	3.5	10	7 PVC/min.
52. W.L. 64, M	—	12 PVC/min.	4.0	10	11 PVC/min.
Average			3.7	11	

failure (Patient 12) had had a history of Stokes-Adams attacks for 5 years. She was refractory to Isuprel, ephedrine, molar lactate, and many other drugs. Autopsy revealed extensive coronary atherosclerosis and myocardial fibrosis, which had almost obliterated the atrioventricular node.

The other 3 patients, who were not on digitalis, had electrocardiographically documented complete heart block of 2 to 5

Effect observed		*Serum calcium (mEq./L.)*		*Serum potassium (mEq./L.)*		*Subjective symptoms*		*Remarks*
Onset (min.)	*Duration*	*Before infusion*	*After infusion*	*Before infusion*	*After infusion*	*Before infusion*	*After infusion*	
12	Permanent	—	—	—	—	0	9	Circumoral paresthesia. Arm pain
5	3 hr.	5.6	4.5	4.0	3.8	++	—	Nausea remitted
5	Permanent	—	—	—	—	++	—	Nausea remitted
7	2 hr.	6.2	5.1	3.8	3.8	—	—	Arm pain
5	1 hr.	—	—	—	—	—	—	Arm pain
10	50 min.	5.8	5.0	4.2	4.2	++	—	Arm pain
8	1 hr.	—	—	—	—	++	—	Epicardial metastasis of carcinoma of breast
8	90 min.	6.4	5.9	3.6	3.6	—	—	Acute thrombosis of right pulmonary artery
—	—	5.9	5.0	3.9	3.9	—	—	Circumoral paresthesia
—	—	—	—	—	—	—	—	Extensive coronary atherosclerosis. Arm pain
—	—	6.1	5.9	4.1	4.0	—	—	Chronic myocarditis and myocardial fibrosis
—	—	5.8	4.9	4.3	4.4	—	—	———
—	—	—	—	—	—	—	—	———
—	—	5.9	4.2	4.0	3.9	—	—	Circumoral paresthesia. Arm pain
7.5		5.8	5.1	4.0	4.0			

years' duration, which was believed to be due to coronary atherosclerosis. These patients were refractory to trials of Isuprel, ephedrine, and lactate. Their response to Na_3EDTA was also uniformly negative.

COMMENT. Thus, with one possible exception (Patient 17), when digitalis was considered to be the cause of the block, infusion of Na_3EDTA was effective. In 3 patients who were suspected of having

long-standing organic atrioventricular nodal disease, and in another in whom there was autopsy proof of nodal disease, the drug was ineffectual.

Atrioventricular dissociation. In 5 patients, atrioventricular dissociation, which was believed to have resulted from absolute digitalis overdosage, converted to normal sinus rhythm (Fig. 4; Table IV). This conversion was either permanent or became permanent when oral potassium was given and digitalis was withdrawn. In this study, all patients who had this arrhythmia were receiving digitalis.

COMMENTS. Infusion of Na_3EDTA produced the same results which would be expected with withdrawal of digitalis in this group.

Atrial fibrillation. Twelve patients with rheumatic or atherosclerotic heart disease were studied. None had evidence of an overdosage of digitalis. Seven were on digitalis preparations; 5 were not. In the digitalized group there was an average increase of 26 per cent (15 to 45 per cent) in the ventricular rate, compared to an increase of 12 per cent (10 to 16 per cent) in the ventricular rate in the undigitalized group (Table V).

One undigitalized patient was not included in this group because of a serum calcium of 12 mEq./L. The cause of her hypercalcemia is as yet undetermined. Her ventricular rate temporarily rose 65 per cent during the infusion of Na_3EDTA.

Patient 28 was also of special interest. This 61-year-old white man had rheumatic heart disease with predominant mitral insufficiency and severe congestive heart failure. He received large doses of digoxin until his ventricular rate was reduced to 75-80 per minute. Quinidine therapy was then started, and after four doses of 0.2 Gm., anorexia, nausea, diaphoresis, and abdominal cramps developed. It was difficult to determine which drug was causing his symptoms. Twenty-five minutes after Na_3EDTA was administered, all subjective symptoms relented and the ventricular rate increased 15 per cent. Na_3EDTA was continued for another hour, without return of the subjective complaints. Digitalis was temporarily withdrawn, oral potassium chloride was given, and quinidine was continued. The patient's rhythm converted to normal sinus rhythm on 0.4 Gm. of quinidine every 2 hours 5 times daily. It was considered that the administration of Na_3EDTA helped in differentiating between quinidine and digitalis intoxication.

COMMENT. In digitalized patients the increase in ventricular rate was greater, possibly as a result of lessened atrioventricular block, although, as indicated in Fig. 5, other mechanisms may be operative. The same effect would be expected upon withdrawal of digitalis.

Premature ventricular contractions. Eight digitalized and 6 undigitalized patients with premature ventricular contractions, bigeminy or trigeminy, received Na_3EDTA. Six of the 8 patients on digitalis who had clinical evidence of absolute overdosage of digitalis demonstrated a decided decrease in the number of premature ventricular contractions as noted in the electrocardiogram (Fig. 5; Table VI). Of the 2 patients who did not improve, one demonstrated epicardial metastases from carcinoma of the breast at autopsy, whereas in the other, recent thrombosis of the right pulmonary artery was present.

In the undigitalized group a significant improvement was observed in one patient (Patient 50). Autopsy was performed on 2 patients in this group (Patients 48 and 49). Patient 48 had extensive coronary atherosclerosis, and Patient 49 had chronic myocarditis with extensive fibrosis.

COMMENT. In several instances in which digitalis overdosage might have been implicated as the myocardial irritant, Na_3EDTA was effective. In one undigitalized patient, Na_3EDTA was effective. In 4 patients in whom treatment failed, autopsy revealed pathology which might have accounted for the myocardial irritability.

Effect of Na_3EDTA on patients with normal hearts. Twelve undigitalized patients with clinically normal hearts were studied. There was no change in the P-R interval in 11 of the 12 patients studied; in one patient there was a decrease of 0.02 second (0.18 to 0.16 second). A slight increase in heart rate was uniformly present.

Other arrhythmias. A well-digitalized patient with Wolff-Parkinson-White syndrome received 3.0 Gm. of Na_3EDTA without an effect on the delta vector, rate, P-R interval, or other ECG manifestations.

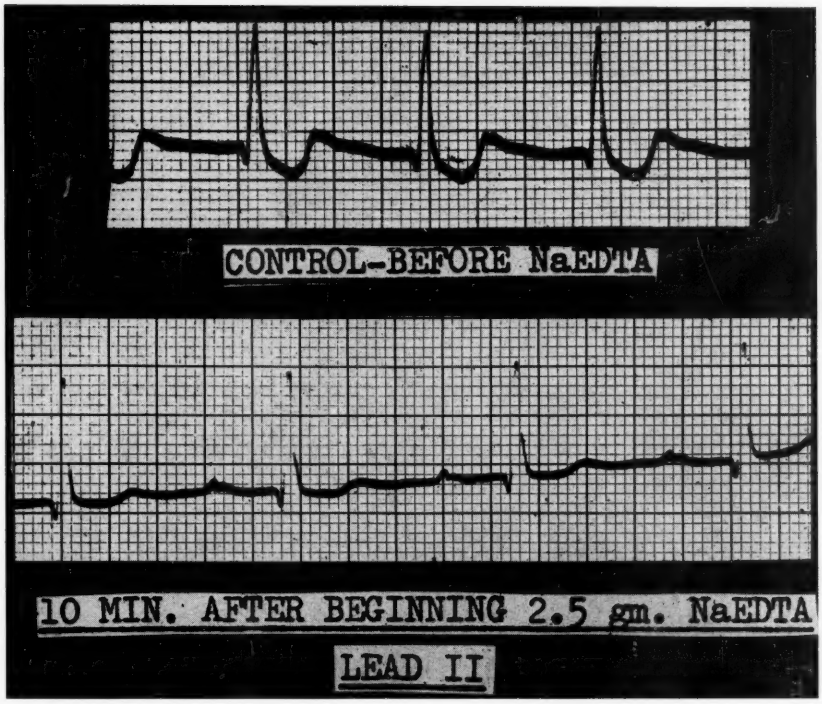

Fig. *1*. A.J. (Patient 5). Marked first-degree A-V block with an initial P-R interval of 0.48 sec. and depressed S-T segments in the control tracing. After 2.5 Gm. of Na_3EDTA the P-R interval becomes 0.32 sec. and the S-T segment approaches normal. The heart rate has gone from a control of 84/min. to 64/min.

BEFORE NaEDTA
AFTER 1.0 gm. NaEDTA - 20 MIN. AFTER INFUSION BEGUN
AFTER 1.2 gm. NaEDTA - DURING TETANY - 30 MIN. AFTER INFUSION BEGUN
IMMEDIATELY FOLLOWING 2 cc. 10% CALCIUM GLUCONATE I.V.
ALL LEAD II

Fig. *2*. M.W. (Patient 10), a 9-month-old Negro boy with renal and cardiovascular anomalies who had received, by error, 10 times his calculated maintenance dose of digoxin. In the upper tracing, the patient developed a varying A-V block. After 1.0 Gm. of Na_3EDTA, sinus rhythm returned. After 1.2 Gm. of Na_3EDTA, tetany developed and sinus arrest with a slow idionodal rhythm ensued. Immediately after 2 c.c. of 10 per cent calcium gluconate intravenously, irreversible chaotic ventricular rhythm and death occurred.

Two digitalized patients with premature atrial contractions failed to respond, and at autopsy, one had a large right atrial mural thrombus.

Effect of Na_3EDTA on the subjective complaints of digitalis-intoxicated patients. Fourteen of the 36 patients with digitalis intoxication had visual color disturbances, anorexia, nausea, vomiting, diaphoresis, or apathy in varying combinations. All of the patients experienced relief of symptoms during infusion of Na_3EDTA; such relief usually occurred before a change in the arrhythmia.

Pain in the arm above the site of infusion occurred in 26 (40 per cent) of 66 patients and was ameliorated by warm packs or massage of the site of the pain, and occasionally by slowing or diluting the infusion.

No significant, consistent change in blood pressure occurred. All changes were within the limits of error of the cuff technique; the exceptions were in 3 apprehensive patients who had a 25 per cent elevation in systolic blood pressure.

Discussion

Although calcium was recommended in the treatment of heart ailments over a century ago (Blake,[5] 1841), it was Ringer,[6] Howell,[7] and Boehm[8] who delineated our understanding of the effects of calcium and other electrolytes on cardiac action.

The present clinical use of calcium was dramatically introduced in 1928, when an Englishman by the name of Lloyd[9] attached himself to an electrocardiograph and gave himself an intravenous injection of 8 c.c. of 10 per cent calcium chloride. Within a minute of the time of injection he developed a sensation of warmth which progressed to dizziness, pupillodilatation, upward deviation of the eyes, extensor spasm, rigor of the masseters, and respiratory failure. Simultaneous with these events, the electrocardiogram demonstrated frequent extrasystoles, ventricular fibrillation, and then no oscillations at all. His colleagues pounded on his chest and injected intracardiac epinephrine. After 5 minutes of asystole the heart began to beat again. After this experience, Dr. Lloyd edited a lucid paper on the dangers of intravenous calcium, and it might be added that his name has since been notably absent from the literature on this subject. Recent investigations have substantiated his findings.

From the time of Lloyd, there has been an extensive investigation into the role of calcium in cardiac action, although much remains to be learned at the myocardial cellular level.

Currently, it is believed that the effect of digitalis and calcium is at the level of the cell membrane, where it produces a change in permeability which causes a migration of potassium from the cell.[10] Animal experiments demonstrate a negative potassium balance in the coronary circulation during digitalization.[11] This negative balance can be exaggerated by digitalis overdosage.

It is the feeling of Blackmon[11] that available circulating potassium in the case of digitalis intoxication is adequate, but that it cannot enter the cell because of alterations in the cell membrane.[12] Na_3EDTA can reverse digitalis-induced arrhythmias. It is postulated that this is accomplished by binding the calcium ion and thus depotentiating digitalis, which then permits the return of endogenous potassium into the potassium-depleted myocardial cell.

We believe that one of the most important factors in the success of this form of testing is the size of the Na_3EDTA dose and the rapidity with which it is given. In our experience, a test should not be considered to be negative unless the patient has received at least 3.0 Gm. of Na_3EDTA in less than 12 minutes, or unless clinical evidence of hypocalcemia develops. If Chvostek's sign develops, it is probably of more significance in determining the degree of binding of the ionized calcium than are levels of serum calcium ascertained in the laboratory. We believe that low dosage and slow administration are the reasons for the failure to reverse the conduction disturbances in Patient 18, and may well account for some treatment failures by other investigators[13,14] who have used smaller doses over longer periods.

The evaluation of results with premature ventricular contractions, because of the variability, is more difficult than with other more stable rhythms. In our experience, these conduction aberrations are much more elusive and inconsistently related to Na_3EDTA therapy.

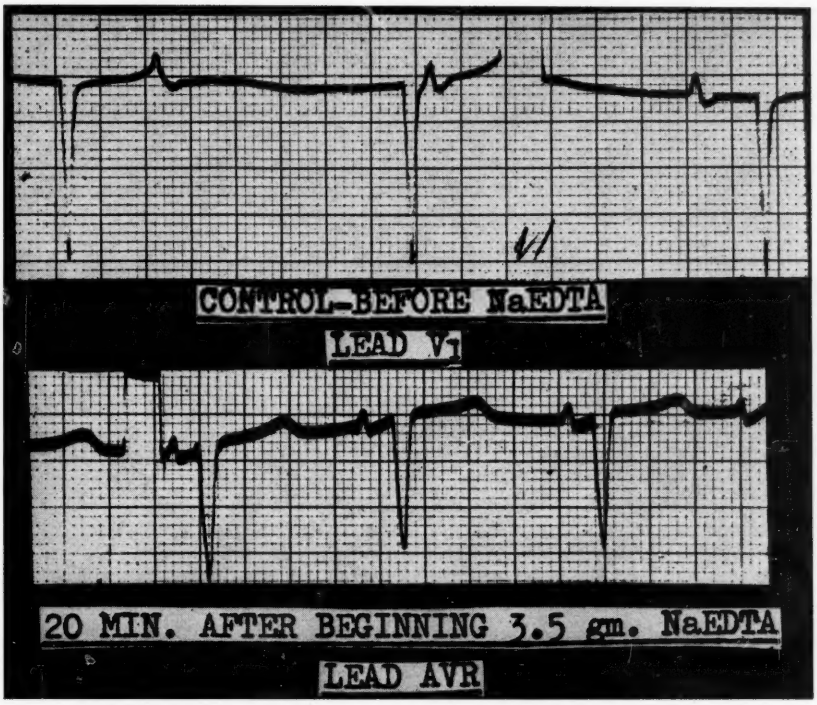

Fig. *3.* A.B. (Patient 15), a 60-year-old Negro who had received an additional 0.5 mg. of digoxin over his maintenance dosage. The patient developed complete heart block 6 hours later. After a 20-minute infusion of 3.5 Gm. of Na_3EDTA the patient developed sinus rhythm.

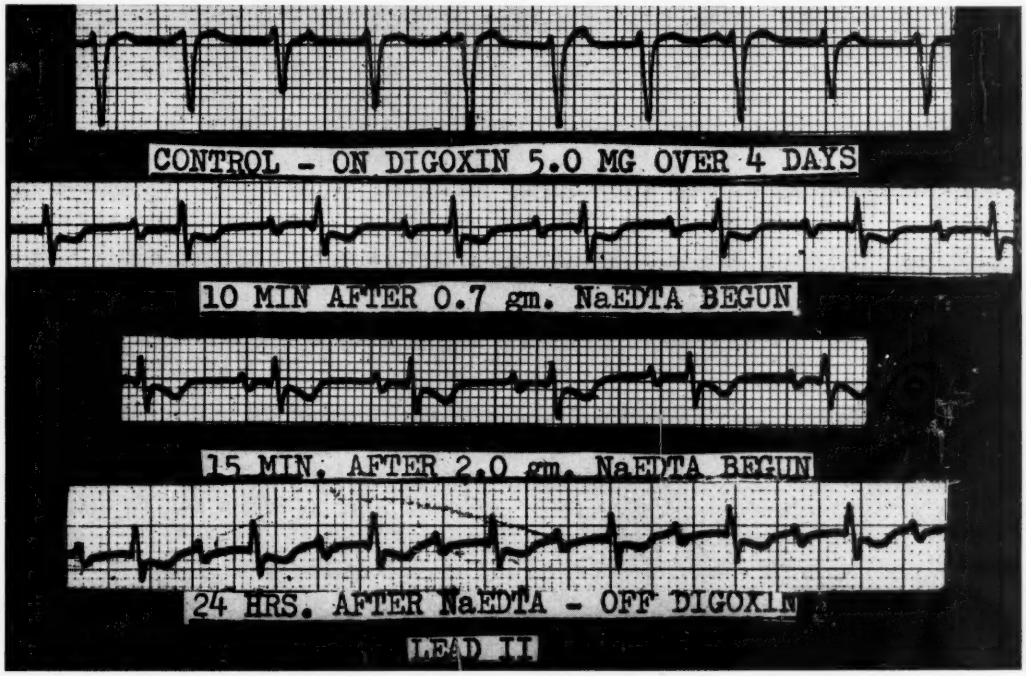
CONTROL - ON DIGOXIN 5.0 MG OVER 4 DAYS
10 MIN AFTER 0.7 gm. NaEDTA BEGUN
15 MIN. AFTER 2.0 gm. NaEDTA BEGUN
24 HRS. AFTER NaEDTA - OFF DIGOXIN
LEAD II

Fig. *4.* E.S. (Patient 23), a 48-year-old white woman who received 5.0 mg. of digoxin over a period of 4 days while in renal shutdown. The patient developed A-V dissociation, which reverted to first-degree A-V block (P-R of 0.24 sec.) within 15 minutes of beginning an infusion of 2.0 Gm. of Na_3EDTA. Twenty-four hours therafter, first-degree A-V block was more pronounced, but A-V dissociation did not return (only uppermost tracing is Lead V_1).

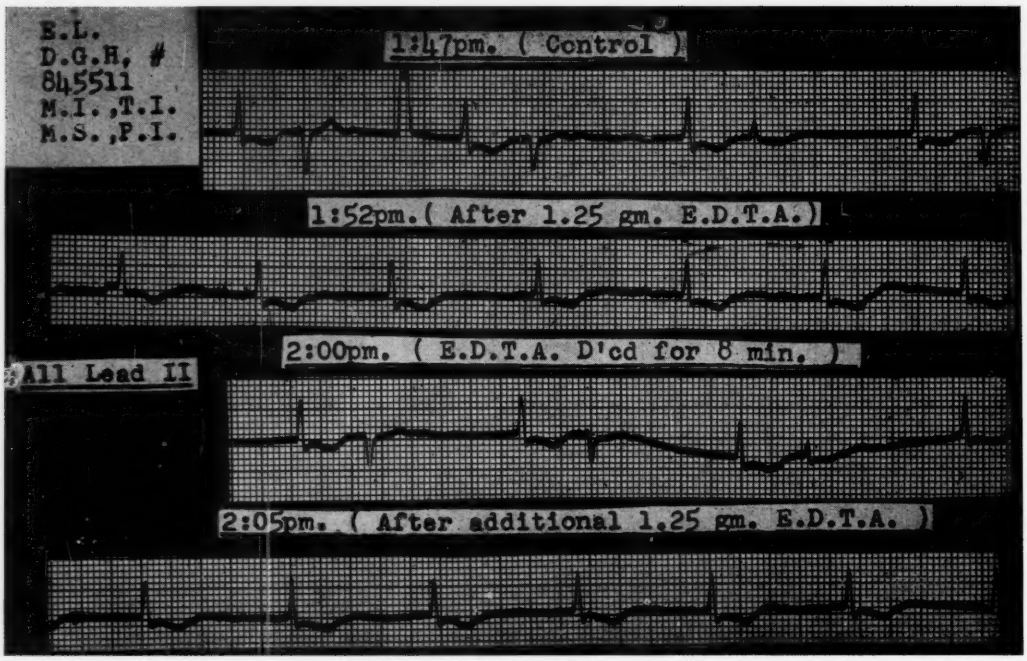

Fig. 5. E.L. (Patient 40), a 58-year-old white woman with rheumatic heart disease, atrial fibrillation, and congestive heart failure who had taken 0.3 mg. of digitoxin over her usual maintenance dosage. Within 24 hours she developed bigeminy; this disappeared 5 minutes after 1.25 Gm. of Na_3EDTA was given, and the infusion was stopped immediately. The bigeminy returned within 8 minutes, and the effect was repeated with an additional 1.25 Gm. of Na_3EDTA.

Out of the 66 patients treated, there were only 3 patients who had no evidence of absolute digitalis overdosage and did respond to Na_3EDTA. Lack of response to Na_3EDTA in 2 of the 3 who did have evidence of absolute digitalis overdosage could well be explained on the basis of slow infusion and inadequate dosage. Six patients who failed to respond were found at autopsy to have evidence of cardiac pathology, which alone could have accounted for the arrhythmia.

Subjective symptoms of digitalis intoxication, when present, responded in all patients. In every patient in whom the arrhythmia or conduction disturbance permanently or temporarily responded to intravenous Na_3EDTA, the withdrawal of digitalis and addition of oral potassium chloride maintained the response. Thus, the drug was an excellent means of predicting the effectiveness of withdrawal therapy, which usually requires days to evaluate.

In our experience, the drug has been relatively ineffective in the treatment of arrhythmias due to causes other than digitalis, but it is still too early to be certain as to its value in differentiating between "organic" arrhythmias and those induced by digitalis, or calcium-potentiating situations. Its effect is so transient in many instances that it is often not a practical therapeutic tool, but does appear to have great value in predicting the efficacy of administration of oral potassium and withdrawal of digitalis.

Na_3EDTA has been implicated as a renal toxic agent in much higher doses given over longer periods.[15] Hemorrhagic diatheses are also reported,[15] but the major clinical danger is tetany. This is a rare occurrence, seen only once in 92 separate infusions. However, if tetany occurs, it would appear advisable to withhold intravenous calcium, if at all possible, since the myocardium appears to be acutely sensitive to calcium under these circumstances.

Summary and conclusions

1. Sixty-six patients who ranged in age from 9 months to 90 years received 92 infusions of trisodium ethylenediamine tetraäcetate (Na_3EDTA) in the treatment of

cardiac arrhythmias or conduction disturbances. Twelve of these patients, however, had no evidence of cardiac disease, arrhythmia, or conduction disturbances. Thirty-six patients were digitalis intoxicated. Eighteen had arrhythmias and were not receiving digitalis.

2. Na_3EDTA was effective in treating arrhythmias in most digitalis-intoxicated patients, but the drug was more unreliable in the treatment of arrhythmias in undigitalized patients.

3. When Na_3EDTA was effective, permanently or transiently, in reversing the arrhythmia, withdrawal of digitalis plus administration of oral potassium chloride perpetuated or reinstituted normal sinus rhythm.

4. Our findings indicate that, in adults, a minimum of 3.0 Gm. of Na_3EDTA should be given within 12 minutes, if possible, before a result is considered to be negative. It is postulated that low dosage over prolonged periods may account for the variability in results by other authors.

5. Tetany occurred in one severely intoxicated 9-month-old child, who died of irreversible ventricular fibrillation when intravenous calcium was given. We caution against the dangers of intravenous calcium in this particular circumstance.

6. The subjective complaints of digitalis-intoxicated patients were relieved during the infusion in all 14 patients in whom the problem existed. This effect usually preceded and predicted the normalization of the ECG relative to the digitalis-induced effect.

7. Six patients whose arrhythmias or disturbances in conduction were refractory to Na_3EDTA died and were autopsied, and both gross and microscopic pathology of the conduction system was found which could have accounted for the arrhythmia produced.

8. Arm pain, circumoral paresthesia, and apprehension occurred in 40 per cent of the patients. The arm pain was readily relieved by massage and warm packs. The other symptoms could be relieved by slowing the rate of the infusion.

We are indebted to Edward Genton, M.D., Howard Horsley, M.D., Samuel Kinard, M.D., and Michael McNalley, M.D., for their cooperation and assistance.

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The vectorcardiogram before and after myocardial infarction
Superimposition of serial loops

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Vectorcardiographic diagnosis of myocardial infarction depends upon the demonstration that the electrical forces of ventricular depolarization differ in a particular way either from a normal or an abnormal pattern (e.g., left ventricular hypertrophy), or from a pattern known to have existed previously in the same patient.[1-3] Authority for the former derives in part from electrocardiographic and vectorcardiographic patterns established by painstaking correlation with autopsy material. Changes which occur in association with clinical episodes of acute myocardial infarction lend additional validity to the belief that certain patterns do, in fact, represent infarction of the myocardium. This report deals with 19 cases in which vectorcardiograms were obtained before and after myocardial infarction.

Material and methods

The vectorcardiogram lends itself to a study of changes by superimposition of serial tracings. Vectorcardiograms taken on 10 patients (Group I) before and after the occurrence of a first myocardial infarction were studied in this manner (Cases 1-10; Tables I and III). The vectorcardiographic loops were transferred to white cards by their projection through a photographic enlarger. Accurate superimposed reproductions were obtained in this way (Figs. 1-6). This provided a practical method of detecting changes which appeared in association with a first clinical myocardial infarction. One of the "control" vectorcardiograms was normal, one was abnormal but not diagnostic, and 8 displayed left ventricular hypertrophy, intraventricular block, right bundle branch block, and right ventricular hypertrophy (Table I).

Similar studies were carried out in 9 additional patients (Group II) with a past history of myocardial infarction when first seen. These patients subsequently suffered a second myocardial infarction (Cases 11-19; Tables II and IV). In this group, the first vectorcardiogram displayed signs of the old infarct, and the second one, changes associated with the observed clinical episode of recurrent infarction. All tracings in this group displayed signs of left ventricular hypertrophy (Table II).

In each case, three pairs (horizontal, sagittal, and frontal) of superimposed "be-

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Received for publication Dec. 1, 1960.
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fore" and "after" loops, as well as electrocardiograms, and orthogonal leads X, Y, and Z* were obtained.

Autopsy was performed in 4 of the 19 patients, and in all of these the vectorcardiographic diagnosis was confirmed.

All vectorcardiograms were recorded by means of the double-cube reference system with positive polarity. The instruments and recording techniques have been described elsewhere.[6]

Results

The results are summarized in Tables I-IV. Changes associated with clinical infarction occurred in at least two of the three orthogonal leads, X, Y, and Z in each of the 19 cases (Tables I and II). The Z axis was modified in 16 cases, the Y axis in 17, and the X axis in 16. Changes were seen in the initial and/or early part of the loops in all cases. The end or terminal appendage tended to be more stable. In Case 14 the only change was reversal in the direction of inscription of the initial forces in the horizontal projection (Y axis). The direction of inscription of the initial forces changed from counterclockwise to clockwise in the horizontal plane in 10 cases, and in the frontal plane in 12 cases. A change in direction of inscription of the body in the horizontal QRS loop occurred in 5 cases, and in the frontal projection in 9 cases.

Inferior orientation of the initial forces was present prior to infarction in all 10 of the cases of Group I, and reversal to superior orientation occurred in 9 of them, 16 to 33 time markings from the 0 point.† Initial forces with superior orientation appeared for the first time in 6 of the 10 cases (Cases 1, 4, 5, 7, 8, and 9; Table I) in association with the first clinical episode of myocardial infarction. In 3 additional cases the initial vectors continued to point downward after clinical infarction occurred, but reversed to superior orientation much earlier in the QRS interval, i.e., 7, 9, and 5 time markings from the 0 point, as compared to 22, 16, and 24 markings, respectively, in the preinfarction vectorcardiograms (Cases 2, 3, 6; Tables I and III, and Fig. 1). Vectorcardiographic signs of inferior myocardial infarction were present in all 9 cases.

Only in Case 10 of those with a first infarct was an isolated anterior wall lesion present, and the sole vectorcardiographic change was increased posterior displacement of the body early in the QRS interval (Fig. 2).[5] Diagnostic signs of anterior infarct were observed in 5 additional cases of Group I (Cases 1, 2, 3, 6, and 7): increased posterior displacement early in the loop in Case 1 (Fig. 3), change to an entirely

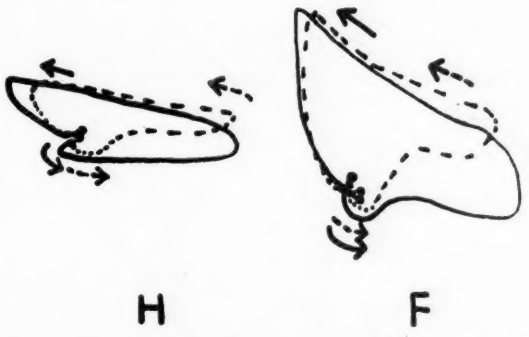

Fig. *1.* Case 3. The first vectorcardiogram shows left ventricular hypertrophy; the second one shows anterior, inferior, septal, and lateral myocardial infarction.
Key: In Figs. 1-4, the solid line = horizontal (*H*) and frontal (*F*) projections prior to infarction, and the broken line = the vectorcardiographic projections after a first infarct. In Figs. 5 and 6, the solid line vectorcardiograms were recorded after a first infarct, and the broken line vectorcardiograms after a second infarct. Solid arrows indicate direction of inscription of solid-line vectorcardiograms, and the broken arrows, the broken-line vectorcardiograms.

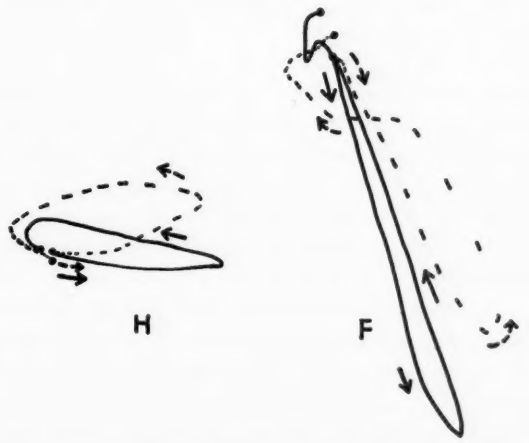

Fig. *2.* Case 10. The first vectorcardiogram shows left ventricular hypertrophy; the second one shows the signs of anterior myocardial infarction. (See *Key* to Fig. 1.)

*X axis: Right-left. Y axis: Posterior-anterior. Z axis: Superior-inferior.
†Each time marking equaled 0.0025 second.

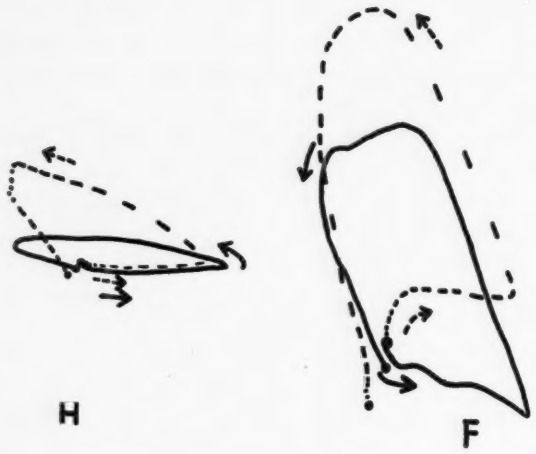

Fig. *3.* Case 1. Changes diagnostic of anterior and inferior myocardial infarction appear in association with a first myocardial infarction. The changes are confined to the early portion of the QRS loop. (See *Key* to Fig. 1.)

Fig. *4.* Case 7. The first vectorcardiogram is characteristic of right ventricular hypertrophy; the second one shows anterior, inferior, and septal myocardial infarction. Right bundle branch block has appeared in the second vectorcardiogram. The QRS interval of the first vectorcardiogram is 0.085 second; that of the second one is 0.115 second. (See *Key* to Fig. 1.)

posterior position of the body of the QRS loop in Cases 2, 6, and 7 (Fig. 4), and concavity of the centrifugal limb in Case 3 (Fig. 1). The alterations were especially striking in Case 7, in which the preinfarction vectorcardiogram showed signs of right ventricular hypertrophy (Fig. 4).

Increased magnitude of various measurements and reorientation of initial and/or early forces also occurred in association with a second clinical infarct (Group II). In Cases 11, 13, 17, 18, and 19, first observed after an anterior infarction had occurred, the QRS forces were inferior for the first 19, 14, 16, and 24 time markings in Cases 11, 13, 17, and 18, respectively; in Case 19 the entire QRS loop was inferior. In all 5 cases a second clinical episode of myocardial infarction occurred, this time in the posterior wall, and the initial forces were observed to change from inferior to superior orientation in each instance (Figs. 5 and 6; Table IV).

Thus, in the combined series of 18 cases of inferior infarction, orientation of the earliest forces changed from inferior to superior in 11 in association with clinical infarction. Almost all measurements of the initial or early superiorly oriented forces were abnormal in the 18 cases with inferior infarct in Groups I and II (Cases 1-9, 11-19)[4]: the sweep was greater than the upper limit of normal (mean +2 standard deviations) in 16, the superior-inferior ratio in 17, the duration of the initial or early superior forces in 17, and the maximal

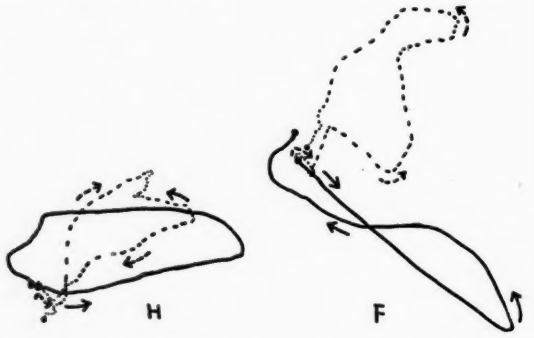

Fig. *5.* Case 19. The first vectorcardiogram displays anterior infarction; the second one shows anterior, inferior, septal, and lateral myocardial infarction. The QRS interval in the second vectorcardiogram has increased from 0.092 to 0.187 second, because of the development of nonspecific intraventricular block. (See *Key* to Fig. 1.)

Fig. *6.* Case 13. The solid-line vectorcardiogram displays anterior and septal myocardial infarction; the broken-line vectorcardiogram displays inferior and lateral, in addition to the anterior and septal, infarcts. The terminal part of the QRS loop has changed significantly. The QRS interval of the first vectorcardiogram is 0.085 second; that of the second one is 0.102 second. (See *Key* to Fig. 1.)

superior vector in 7 cases.[1] In association with a second infarct the earliest forces increased or decreased in magnitude, presumably depending on the location of the old and new lesions in respect to each other; the occurrence of anterior infarction in a patient with a previous posterior wall lesion caused a decrease in the magnitude of the diagnostic measurements associated with the old infarct (Case 16; Table IV).

The earliest forces in the frontal plane were counterclockwise in 8 of the 9 cases (Cases 1-6, 8, 9) prior to the occurrence of primary inferior infarction, but changed to

Table I. *Vectorcardiographic data in Cases 1-10*

Case number	*Changes in X, Y, Z axes*	*Orientation of earliest forces*		*Direction of inscription*				*VCG Dx*	
				Earliest forces		*Body*			
		1st	*2nd*	*1st*	*2nd*	*1st*	*2nd*	*1st*	*2nd*
1.	Y− Z−	LAD	LAU	cc (H) cc cc (F) c		cc (H) cc cc (F) cc		LVH	LVH Ant, Inf
2.	Y− Z−+	RAD	RPDU	cc (H) c cc (F) c		cc (H) cc cc (F) cc		LVH I.V. block	LVH I.V. block, Ant, Inf, Sept
3.	Y− Z−	RAD	LADU	cc (H) cc cc (F) c		cc (H) cc cc (F) cc		LVH	LVH Ant, Inf, Sept
4.	X− Z−	LAD	RAU	cc (H) c cc (F) c		cc (H) cc cc (F) c		Normal	Inf Sept
5.	X−+ Y−+ Z−	RAD	RAU	cc (H) cc cc (F) c		cc (H) cc cc (F) c		Abnormal Not diagnostic	Inf
6.	X+− Y− Z−	RAD	LADU	cc (H) c cc (F) c		cc (H) cc cc (F) c		LVH	LVH Ant, Inf Sept
7.	X+− Y−+ Z−	LAD	LPU	c (H) c c (F) c		c (H) cc c (F) c		RVH	Ant Inf Sept, RBBB
8.	X− Y− Z−	RAD	RAU	cc (H) cc cc (F) c		cc (H) cc cc (F) c		LVH	LVH Inf
9.	X− Y+ Z−	LAD	RAU	cc (H) cc cc (F) c		cc (H) cc cc (F) cc		LVH RBBB	Inf, Sept Lat high post, RBBB
10.	X− Y−	LAD	LAD	cc (H) cc cc (F) cc		cc (H) cc cc (F) cc		LVH	Ant

Key to Tables I-IV: X: Right-to-left axis. Y: Anteroposterior axis. Z: Vertical axis. −: Change to superior or increased superior forces in Y and Z, to the right in X and Z, and posteriorly in X and Y. +: Changes in opposite direction in X, Y, and Z axes. IF: Initial forces. R, L, A, P, U, D: Right, left, anterior, posterior, superior, inferior. 8: Figure-of-8 configuration of QRS. c: Clockwise. cc: Counterclockwise. H, S, F: Horizontal, sagittal, and frontal projections, respectively. 1st, 2nd: First and second vectorcardiograms, respectively. TA: Terminal appendage. LVH, RVH: Left and right ventricular hypertrophy, respectively. I.V. block: Intraventricular block. RBBB, LBBB: Right and left bundle branch block, respectively. Inf, Ant, Sept, Lat, High post: Inferior, anterior, septal, lateral, and high posterior myocardial infarction, respectively. ″: Time markings (each one = 0.0025 second). Angle α H: Angle in horizontal plane subtended by largest vector and horizontal line passing through 0 point. When the largest vector is anterior to this line, the angle is positive; when posterior, it is negative. Angle α F: Angle in frontal plane subtended by largest vector and horizontal line passing through 0 point. When the largest vector is inferior to this line, the angle is positive; when superior, it is negative.

Table II. Vectorcardiographic data in Cases 11-19

Case number	Changes in X, Y, Z axes	Orientation of earliest forces		Direction of inscription				VCG Dx	
				Earliest forces		Body			
		1st	2nd	1st	2nd	1st	2nd	1st	2nd
11.	X− Z−	RAD	RAU	cc (H) c cc (F) c		8 (H) 8 cc (F) 8		LVH Ant	LVH Ant, Inf, Lat
12.	X− Y− Z−	RAU	RPU	cc (H) c c (F) c		cc (H) c c (F) c		LVH Inf	LVH Ant Inf, Sept, Lat
13.	X− Y−+ Z−	LAD	LPU	cc (H) c cc (F) c		cc (H) c cc (F) c		LVH Ant Sept	LVH Ant, Inf Sept (high post?)
14.	X+ Y−	RAD	RAD	cc (H) c c (F) c		cc (H) cc cc (F) cc		LVH Ant, Inf, Lat	LVH Ant, Inf, Sept, Lat
15.	X− Y− Z−+	RAU	RPU	cc (H) c c (F) c		cc (H) cc 8 (F) c		LVH Inf	LVH Ant Inf, Sept
16.	X+ Y−+	LAU	LPU	cc (H) cc c (F) c		cc (H) cc c (F) c		LVH Inf	LVH Ant, Inf, Sept
17.	X−+ Y+ Z−	LAD	RPU	cc (H) c cc (F) c		8 (H) c cc (F) c		LVH Ant	LVH Ant Inf, Sept, Lat, Incomplete RBBB
18.	X+ Y+ Z−	RPD	LPU	c (H) cc c (F) c		8 (H) 8 cc (F) cc		LVH I.V. block Ant, Sept	LVH I.V. block Ant, Inf, Sept
19.	X− Y− Z−	LAD	RPU	cc (H) c cc (F) c		cc (H) c 8 (F) c		LVH Ant	LVH Ant, Inf Sept, Lat, I.V. block

For key to table, see Table I.

clockwise inscription in all of them after infarction. In Case 7 with right ventricular hypertrophy the earliest forces displayed clockwise inscription before and after the infarction. The initial forces were counterclockwise in Case 10 before and after the occurrence of anterior myocardial infarction.

In Cases 12, 15, and 16 an anterior wall lesion occurred for the first time with a second clinical episode of infarction. The changes diagnostic of anterior infarction were a shift to a posterior position of the body of the QRS in all 3, clockwise inscription of the initial forces in the horizontal projection in Cases 12 and 15, and clockwise inscription of the body of the QRS in the horizontal plane in Case 12.

Study of the superimposed tracings shows that the general disposition of the QRS loop beyond the early forces depends largely upon the preinfarction morphology of the loop. Striking changes toward the end of the loop did occur, however, in one case (Fig. 6; Case 13). Changes in the terminal loops in the postinfarction vectorcardiograms in Case 7* (Fig. 4) and Case 9* are due to the occurrence of right bundle

*QRS duration in these cases increased as follows from pre- to postinfarction vectorcardiograms: Case 7: 0.085 to 0.115 sec. Case 9: 0.122 to 0.15 sec.

Table III. *Vectorcardiographic data in Cases 1-10*

Case number	Angle α H		Angle α F		Earliest forces (frontal plane)								VCG Dx of infarct
							Change from D to U''		Duration	Maximal	Sup/Inf ratio	Sweep	
	1st	2nd	1st	2nd	1st	2nd	1st	2nd	2nd''	2nd (mv.)	2nd	2nd (mv.)	
1.	− 2°	− 4°	− 85°	− 90°	cc D	c U	20	0	12	.09	00	.29	Inf, Ant
2	− 1	−12	− 87	+ 7	cc D	c DU	22	7	13	.045	1.8	.21	Inf, Ant Sept
3.	0	−12	−109	− 16	cc D	c DU	16	9	5	.04	00	.16	Inf, Ant Sept
4.	+ 2	− 1	−105	− 98	cc D	c U	18	0	10	.21	.51	.15	Inf, Sept
5.	+ 8	+25	+ 75	+ 60	cc D	c U	22	0	11	.12	.35	.07	Inf
6.	− 8	− 8	+ 12	+ 8	cc D	c DU	24	5	13	.03	.30	.51	Inf, Ant Sept
7.	+30	−13	+ 71	+ 43	c D	c U	33	0	8	.05	.50	.055	Inf, Ant Sept
8.	−14	−19	+ 18	+ 30	cc D	c U	Entirely inferior	0	12	.12	.24	.19	Inf
9.	−16	No leftward forces	−105	−115	cc D	c U	19	0	24	.20	00	.06	Inf, Sept Lat High post
10.	+ 5	−20	+ 69	+ 58	cc D	cc D	—	–	—	—	—	—	Ant

For key to table, see Table I.

branch block, and in Case 17* to the development of incomplete right bundle branch block. Right bundle branch block, as is well known, alters the terminal portion of the QRS loop. The changes in Case 19* (Fig. 5) are associated with the appearance of nonspecific intraventricular block.

Discussion

Diagnostic vectorcardiographic signs of myocardial infarction[1-6] were observed to appear in association with episodes of clinical myocardial infarction. The technique of superimposition of serial vectorcardiographic loops proved to be eminently useful in demonstrating the diagnostic changes, comprising, for the most part, the earliest superiorly oriented forces in inferior myocardial infarction and increased magnitude of posterior vectors located within 0.045 second after onset of the QRS loop in anterior infarction.

As a result of our previous studies, diagnostic importance was attached to orientation and direction of rotation of initial and early QRS forces, rotation of the body of the QRS loop, duration of early

*QRS duration in these cases increased as follows from pre- to postinfarction vectorcardiograms: Case 17: 0.092 to 0.11 sec. Case 19: 0.092 to 0.187 sec.

Table IV. *Vectorcardiographic data in Cases 11-19*

Case number	Angle α H		Angle α F		Earliest forces (Frontal plane)												VCG Dx of infarct	
							Change from D to U"		Duration		Maximal		Sup/Inf ratio		Sweep			
	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd (mv.)	1st	2nd	1st	2nd (mv.)	1st	2nd
11.	−18	−10	+ 6	+ 5	cc D	c U	19	0		16		.065		1.0		.115	Ant	Inf, Ant, Lat
12.	− 2	0	+22	+52	c U	c U	0	0	9	16	.09	.27	.29	.6	.23	.15	Inf	Inf, Ant, Sept Lat
13.	−20	−12	+ 3	− 7	cc D	c U	14	0		14		.17		1.2		.30	Ant Sept	Inf, Ant, Sept High post?
14.	−17	−38	−98	−71	c D	c D	8	9	8	8	.07	.11	00	00	.25	.22	Inf Ant Lat	Inf, Ant Sept, Lat
15.	− 3	− 8	+22		c U	c U	0	0	6	12	.08	.18	.09	.45	.18	.30	Inf	Inf, Ant Sept
16.	− 4	− 4	+32	+28	c U	c U	0	0	6	6	.06	.04	.16	.08	.13	.07	Inf	Inf, Ant Sept
17.	−20	− 1	−38	+65	cc D	c U	16	0		15		.32		.59		.24	Ant	Inf, Ant Sept, Lat
18.	−30	− 9	+ 4	−88	c D	c U	24	0	0	26+		.49		00		.44	Ant Sept	Inf, Ant Sept
19.	−13	−34	+36	−45	cc D	c U	Entirely inferior	0		11		.09		2.4		.16	Ant	Inf, Ant Sept, Lat

For key to table, see Table I.

superior forces, and magnitude of superior and posterior vectors. The magnitude of certain vectors may be the only distinction between the noninfarct vectorcardiogram and that of anterior and posterior myocardial infarction. Superimposition of serial vectorcardiograms, a method of demonstrating vectorcardiographic changes not previously exploited, has emphasized the validity of these empirical diagnostic features. Such an apparently trivial feature as clockwise inscription of initial forces has acquired greater diagnostic validity by the demonstration of its appearance during a clinical episode of acute myocardial infarction. This is also true of the other diagnostic features discussed above. The superimposition technique thus helps to validate these diagnostic features of infarction of the myocardium. In some cases of second infarct the only change is in the magnitude of the abnormal vectors, and the vectorcardiographic diagnosis of recurrent infarction can be made best by the superimposition technique.

The time of change from inferior to superior orientation of initial forces has been shown to be a reliable sign of inferior infarction. However, the change in orientation may not begin at the 0 point, but at a variable time interval beyond it, a pattern which is also observed in noninfarct vectorcardiograms. It is noteworthy that prior to the occurrence of infarction the briefest interval from the onset of ventricular depolarization to reversal from inferior to superior orientation is 0.04 second, and that after the development of inferior infarction the longest corresponding interval is 0.02 second. Vectors which change to superior orientation later than 0.02 second after the 0 point are not classified as earliest forces and are not diagnostic of infarction.

It is generally agreed that diagnostic signs of myocardial infarction are located in the early depolarization forces, and our data clearly confirm this opinion. However, changes in the later or terminal portion of the depolarization loop have been observed, and it has been suggested that diagnostic signs may be found in this part of the vectorcardiogram.[7] Striking changes in this portion of the vectorcardiogram were observed in one of our cases, in which the question of high posterior infarct was raised. Such a lesion, located in the posterobasal region of the left ventricle, would affect the terminal portion of the QRS loop if this region were the last fraction of myocardium to be depolarized. Changes in other cases were associated with the development of intraventricular block or were minor and not significant for the following reasons: (1) There is a certain amount of variability from day to day and even from loop to loop at the same recording. (2) The configuration of the terminal portion is, to some extent, conditioned by the earlier vector. (3) Myocardial infarction affects the S-T junction. Thus, the changes which occur in the terminal portion of the loop may indeed be the result of infarction, but, in our experience, do not help in diagnosis and localization.

Summary and conclusions

1. The diagnostic signs of myocardial infarction were studied by superimposition of vectorcardiograms obtained before and after a first myocardial infarction, and before and after a second myocardial infarction.

2. These studies confirm the view that diagnostic signs of infarction occur in the initial and/or early portion of the depolarization loop. Configuration of the rest of the body of the loop and the terminal appendage is largely determined by the preinfarction morphology of the loop.

3. Signs in use in this laboratory for the diagnosis of anterior and inferior myocardial infarction have been shown to appear for the first time in association with clinical acute myocardial infarction.

4. The diagnostic signs of anterior myocardial infarction are increased posterior displacement early in the QRS loop, displacement of the body of the QRS loop to a posterior position, change from counterclockwise to clockwise inscription of the initial forces and the body of the QRS loop in the horizontal projection, and concavity of the centrifugal limb of the QRS loop.

5. The diagnostic signs of inferior myocardial infarction are confined to the initial or early depolarization forces and consist in superior orientation, clockwise inscription, abnormal magnitude and greater than

normal duration, abnormally wide sweep, and greater than normal superior-inferior ratio.

6. Vectorcardiographic signs of infarction in multiple areas may occur in association with a single clinical episode of acute myocardial infarction.

7. Pre-existing signs of myocardial infarction may become less conspicuous after the occurrence of a second myocardial infarction. When the second infarct is in the same location as the first one, the magnitude of the diagnostic signs increases.

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Partial rupture of pulmonary artery with lesions of medionecrosis in a case of mitral stenosis

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Initially, idiopathic medionecrosis was considered to be a local disease of the aorta at the point at which a dissecting aneurysm or a spontaneous rupture had developed (Erdheim[1,2]; Gsell[3]). Later on it was interpreted to be a systemic disease of the elastic arteries (Wolff[4]). Our own findings in two cases of spontaneous partial rupture of the aorta where severe lesions were also observed in peripheral vessels led us to believe that medionecrosis is, in fact, a systemic arterial disease which may attack mainly arteries of the pulmonary circulation, as shown by the case we are describing.

Looking through the cases which have been reported in previous publications, we find that the macroscopic and microscopic aspects of idiopathic medionecrosis, i.e., dissecting aneurysm and spontaneous rupture, and destruction of the elastic tissue, necrosis of the muscle fibers without reaction, increase of the basophilic ground substance, vascularization of the media, etc., as described for the aorta, are also found in the pulmonary artery, although such localization is far less frequent.

Case report

C.M.M., a 27-year-old single woman was hospitalized on account of dyspnea and edema of the lower limbs. The patient had had rheumatic fever at the age of 14 years, with recurrences at 15 and 16. Since her eighteenth birthday the patient had been suffering from dyspnea on exertion, reaching the point of orthopnea, sometimes producing foamy and reddish-colored sputum. There were two reports of hemorrhages. Nocturia and edema of the lower limbs had increased during the last months.

Clinical examination. Cyanosis, red spots on the cheek, and moderate dyspnea were observed. The blood pressure was 100/72 mm. Hg. The objective examination revealed also a diastolic murmur and opening snap at the apex, strong systolic-diastolic murmur (Graham Steell) at the pulmonary focus, and pronounced stasis of the lungs. The liver was enlarged. The lower limbs showed edema.

X-ray examination. The heart was enlarged due to the size of the right ventricle and left atrium. The pulmonary artery showed enormous dilation. Advanced interstitial sclerosis and hemosiderosic nodules were observed.

Electrocardiogram. Marked hypertrophy and overload of the right ventricle could be demonstrated.

The patient showed slight improvement after treatment with cardiac stimulants and diuretics. There were still signs of cyanosis, dyspnea, and subedema of the lung after exertion. Surgical intervention was suggested for valvulotomy. During the operation, carried out on Nov. 22, 1954, with good results from the valvulotomy, the cyanosis increased, spontaneous breathing was not restored, and the patient died from respiratory insufficiency, with cyanosis and coma.

Postmortem diagnosis. The diagnoses were: old endocarditis at the mitral valve with stenosis; dilatation of the left atrium; pulmonary atherosclerosis; partial rupture of the pulmonary artery at the posterior wall; dilatation of the right cardiac cavities and right ventricular hypertrophy; and congestion of the internal organs.

Macroscopic picture of the pulmonary artery. Two centimeters above the pulmonary valve the posterior wall showed a transverse tear (Fig. 1)

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Received for publication Dec. 2, 1960.

Fig. *1.* Partial rupture of the main pulmonary arterial trunk. Macroscopic aspect.

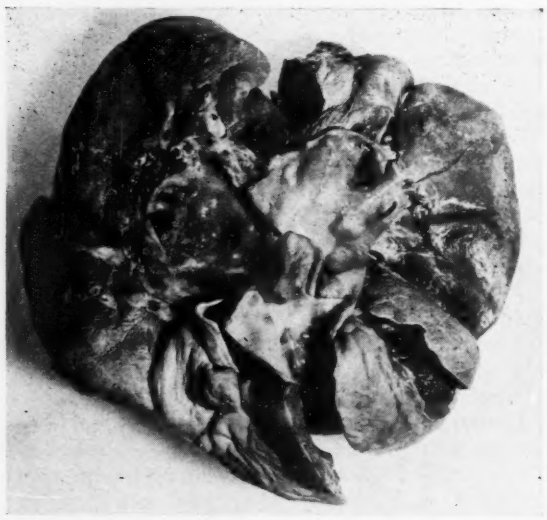

Fig. *2.* Transverse laceration of the trunk and right branch of the pulmonary artery. Macroscopic aspect.

which extended into the right branch (Fig. 2). The lesion was 11 cm. long and 3 cm. high. The edges, round and protruding at the level of the trunk, flattened out toward the distal part of the tear, until they reached more or less the same level as the remaining wall of the artery. Near the rupture the intima was of a translucent and shiny bluish-gray color. Farther away from the lacerated part there were some depressed bluish-gray areas in the intima and lipoid plaques. All the arterial branches showed diffuse dilatation.

Histologic examination of the pulmonary artery. The lesion consisted of a break in the intima and media which extended three quarters of the way through the media (Fig. 3). At this point of the artery the wall was formed by a dense connective tissue and capillaries which were sometimes obviously engorged (Fig. 4), without any smooth muscle fibers or elastic laminae. Only a few of the elastic laminae of the outer layer of the media could be found. In the peripheral area, nearer the edges of the laceration, we did find some smooth muscle fibers and elastic laminae. The appearance of the medial break varied. In places the edge of the tear was round. Elsewhere it was sharp (Fig. 5). Some elastic fibers extended to the margin of the break. Other fibers were thinned and did not quite reach the margin of the laceration (Weigert's elastic tissue stain). Intimal tissue covered the edges and passed into the connective tissue of the tear.

The remaining part of the vessel wall showed some eosinophilic necrotic foci containing no nuclei, several areas without elastic fibers (Fig. 6), and a focal increase of basophilic, metachromatic, and PAS-negative ground substance. Because of the increase in this substance, wider distances between the fibers or formation of small cystic cavities were seen (Fig. 7). Vasa vasorum may have reached the

Fig. *3.* Interruption of the intima and media. Laceration. (Hematoxylin and eosin stain.)

medial third of the media. The intima was thickened, especially in the area in which elastic laminae showed the most intense destruction. Muscle fibers may have participated in the formation of the thickened areas. The adventitia was thickened and partly hyalinized.

The depressed area, seen macroscopically, corresponded to a large medial focus without elastic laminae, covered by a strand of connective tissue which extended into the intima.

Intrapulmonary artery. There was intense thickening of the intima, which contained some foamy cells at several places; a newly formed internal elastic membrane was outlined.

Aorta. No pathologic findings were observed in the aorta.

Discussion

The foregoing description shows that there were severe lesions of chronic medionecrosis (in the sense of Faria[5]), with one of the main characteristics being the destruction of the elastic laminae. Because of this destruction a partial rupture of the artery developed. Proof of the long-standing process was the presence of fibrous scar tissue filling the gap of the laceration. In the depressed area, seen macroscopically, this scar tissue was situated on the same level as the remainder of the media. Another finding which indicated the age of the lesion was the scarcity of recent necrotic foci. Vascularization of the media, thickening of the intima and the adventitia, are further alterations usually found in vessels with medionecrosis. Signs of regeneration of muscle fibers or elastic laminae, sometimes referred to in cases of medionecrosis,[1,2,4] were absent. The alterations of the pulmonary arteries were due to pulmonary hypertension.

On the assumption that the dissecting aneurysm and the spontaneous rupture are the results of the same pathologic process, i.e., medionecrosis, we collected 42 cases (including our own) described in the literature (Table I). Tables II and III show the most important clinical and pathologic findings. We consider this classification to have better morphologic foundations than the definition of spontaneous rupture of the pulmonary artery defended by Brettell[14] and McNaught[10] as a separate disease.

We should like to draw attention to the case described by Duffield,[7] in which a dissecting aneurysm and a spontaneous rupture existed simultaneously in the right

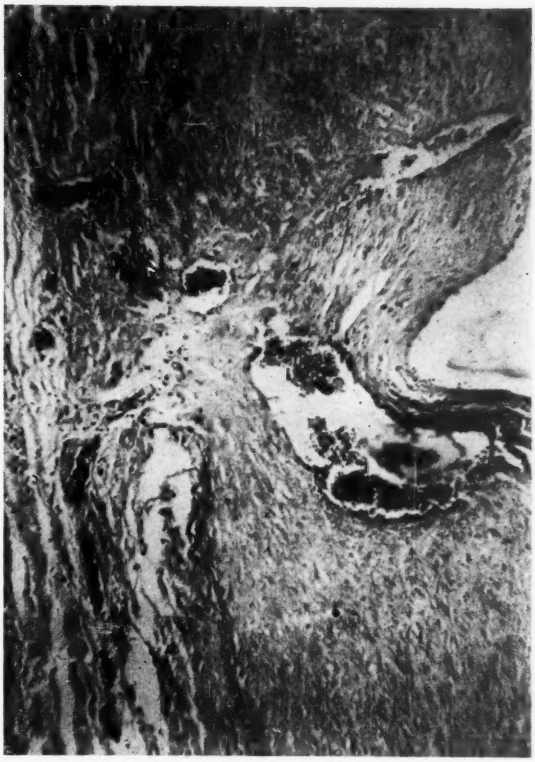

Fig. *4.* Important vascularization of the fibrous scar tissue at the tear of the media. (Hematoxylin and eosin stain.)

Fig. *5.* Sharp edge of the tear. Destruction of the elastic laminae. (Weigert's elastic tissue stain.)

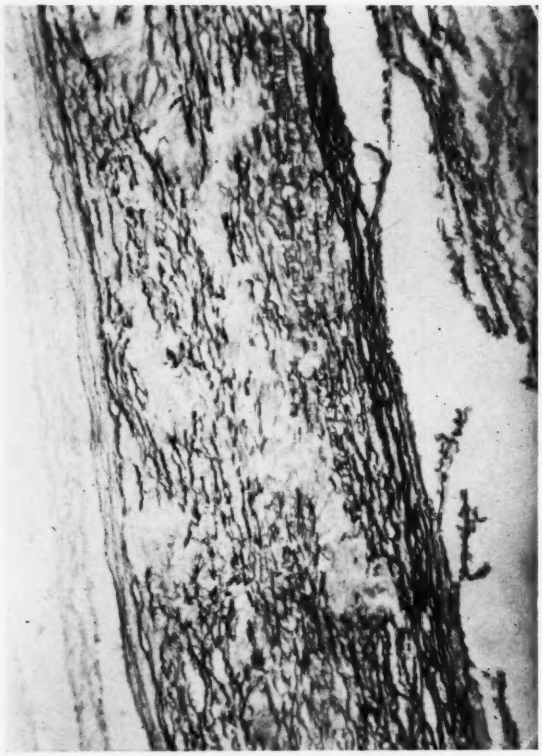

Fig. *6.* Foci of the media without elastic laminae outside the lacerated area, seen macroscopically. (Weigert's elastic tissue stain.)

Fig. *7.* Focus of increased ground substance outside the laceration. (Hematoxylin and eosin stain.)

and left pulmonary arteries. This case confirms our opinion as shown in Table I.

Lindert[28] described the case of a patient with a dissecting aneurysm of the aorta and, at the same time, a spontaneous rupture of the left branch of the pulmonary artery. Of course, this coexistence may be due to mere coincidence.

The case presented by Fowler[22] is doubtful, since the diagnosis was based on nothing but clinical symptoms, which are insufficient for the recognition of this disease.[27] The rupture was a hypothesis offered by the physician to explain the sudden death.

Medionecrosis of the pulmonary artery is a rare disease with no marked preference for either sex, contrary to the findings with medionecrosis of the aorta.[5,31,32] The same difference exists between the aneurysm of the pulmonary arteries and that of the aorta.[27] Medionecrosis of the pulmonary artery occurs most frequently between the ages of 20 and 29 and 40 and 49 years. In the majority of cases the macroscopic lesion is found in the main trunk, followed in frequency by the right branch. The number of cases which show a real aneurysm is far surpassed by the number in which it is absent. Saccular aneurysms are more frequent than the spindle-form variety. Cases in which there is extensive thrombosis are very seldom met with.[14]

Comparing medionecrosis of the pulmonary artery with aneurysm of the same vessel, we find that the latter is also very rare,[11,20,25,26,33] although much more frequent

Table I. *Cases of medionecrosis*

Dissecting aneurysm (total: 15 cases)	
With internal tear	7
Without internal tear	2
With aneurysm	3
Without aneurysm	8
Spontaneous rupture (total: 27 cases)	
Total rupture:	
With aneurysm	11
Without aneurysm	4
Partial rupture:	
With aneurysm	2
Without aneurysm	3

than medionecrosis of the pulmonary artery. It shows no predilection for either sex,[25,27] is localized mostly in the main trunk,[18,22,23] and is described predominantly as saccular[18] or spindle shaped.[25,27] Only by systematic microscopic examination will it be possible to decide whether there is indeed a closer relation between the aneurysm of the pulmonary artery and medionecrosis.

The symptoms vary and depend on the primary disease. Sudden precordial, substernal, or thoracic pain reported in a certain number of cases and occasionally combined with anguish seems to correspond to the rupture. Radiation of the pain into the arms may be present. In one case the radiation of pain into the right arm was related to the rupture of the right branch of the pulmonary artery. Collapse, state of shock, and sudden death are due to the ensuing hemorrhage. In most cases there is a total rupture of the wall, with lethal hemorrhage, especially into the pericardium (Table IV).

Two out of 7 cases without rupture are cases of dissecting aneurysms. The other cases—like the one we observed—can be considered to be partial ruptures. The explanation for the fact that partial rupture seems to be relatively rare is that it does not cause death. When death occurs it is due to concomitant diseases: endocarditis caused by streptococcus infection,[26] and after effects of surgical intervention.[27] Finally, partial ruptures may be incidental postmortem findings.[6] Thus, cases may be easily overlooked, probably because of a lack of histologic examination.

The microscopic lesions—rarely reported—correspond to those of medionecrosis.[8,12,14,15,29,30] From this point of view our case is rather instructive.

We disagree with Brettell,[14] who considers the microscopic findings in cases of "spontaneous rupture of the pulmonary artery" to be similar to those described in aging. We think that there are marked differences between our Fig. 5, for instance, and the findings of Heath,[34] who dealt with the structure of the pulmonary artery at different ages.

The different primary diseases reported in cases of medionecrosis of the pulmonary artery are indicated in Table V. All of them are the consequences of pulmonary hypertension. Among the cases of hypertension caused by congenital abnormalities, we rather frequently find cases of patent ductus arteriosus. Among those due to acquired pulmonary hypertension, mitral stenosis ranks first. Morphologic findings of pulmonary hypertension, such as hypertrophy of the right ventricle and/or pulmonary atherosclerosis, were found in 26 cases. In the others, these alterations cannot be excluded because the case reports are not always sufficiently detailed. The pathogenic factors considered were: bacterial infection,[26] syphilis,[8,9] "chronic deforming inflammation,"[6] rheumatism,[12,18] trauma,[27] atherosclerosis,[11,19,23,30] and pulmonary hypertension.[8,9,12,21,29] Other authors mention hypoplasia[24] or congenital abnormalities[8,9,11,18,25,26] as responsible factors. We should like to point out that the same factors are considered to be responsible for the aneurysm of the pulmonary artery.[18,20,25,27]

With regard to medionecrosis of the pulmonary artery the above-mentioned pathologic situations cannot be considered as being all etiological factors. Some of them, such as trauma, syphilis, rheumatism, and bacterial infection, do not have sufficient foundation and are by no means constant. Endocarditis as mentioned in the Hartwell case[26] may have played some part in the start of the rupture, but there is reason to doubt that it was the only cause. In one of the cases thought to be due to syphilis, the author himself (Neuburger[9]) stressed that the Wassermann reaction was negative and that nothing in the case history could be found to point to syphilis. Atherosclerosis can be considered to be a consequence of the existing pulmonary hypertension rather than a cause of medionecrosis.

The hypertension which is practically constant in cases of medionecrosis of the pulmonary artery has undoubtedly an important part as an etiological factor, perhaps even more so than in cases of medionecrosis of the aorta,[32,35] at least in respect to the localization. The fact that congenital heart disease is found in a relatively large number of cases of medionecrosis might suggest—as an analogy to medionecrosis of the aorta—that there is a congenital fragility of the vascular wall,[30,36] which may. also

Table II. *Dissecting aneurysms*

Author	*Age (yr.)*	*Sex*	*Primary disease*	*Localization*	*Aneurysm*	*Intimal tear*
Helmbrecht, 1842 (cited by Posselt[6])	21	M	Pulmonary hypertension	Main trunk		+
Touze, 1863 (cited by Posselt[6])	49	M		Main trunk	−	
Duffield,[7] 1882	50	F	Pulmonary emphysema	Right branch	+	
Vincenzo,[8] 1904	25	M	Congenital mitral stenosis	Main trunk	Saccular	+
Neuburger,[9] 1930	28	F	Pulmonary tuberculosis, emphysema	Main trunk	−	+
McNaught,[10] 1935	44	F	Mitral and tricuspid stenosis with insufficiency	Main trunk		+
Laubly and Routier,[11] 1941	47	M	Defect of interauricular septa	Main trunk	Spindle shaped	
Foord,[12] 1947	26	F	Patent ductus arteriosus	Main trunk, right branch	−	−
	70	M	Pulmonary tuberculosis, emphysema	Right branch	−	−
Crumpton,[13] 1950	19	M	Common truncus arteriosus with 3 valves, interventricular septal defect, hypoplasia of the aorta (Humphreys type 4)	Main trunk and branches	−	+
Ohela and Teir, 1954 (cited by Brettell[14])	61	M				
	31	M	Cardiac congenital disease, patent ductus arteriosus			
Fleming,[15] 1956	26	M	Common truncus arteriosus, patent ductus arteriosus	Main trunk	−	+
Odinokowa, 1956 (cited by Foord[12])	43	F	Mitral stenosis	Main trunk	−	
Durno and Brown,[51] 1908	33	M	Patent ductus arteriosus	Main trunk	−	+

Atherosclerosis	*RVH*	*External rupture*	*Interpretation*	*Microscopic findings*
+		Hemopericardium	Pulmonary hypertension	——
		+		
+	+	Hemopericardium		
+	+	Hemopericardium	Pulmonary hypertension, congenital abnormality, syphilis	Muscle fibers destroyed, irregularities of elastic fibers, vasa vasorum obliterated
	+	Hemopericardium	Syphilis, hypertension, congenital abnormality	
+	+	Hemopericardium		Increased mucoid material, elastic fibers farther apart and fragmented, muscle fibers decreased in amount, increase of fibrous tissue
+	+		Atherosclerosis, congenital abnormality	
+		Mediastinum		Elastic laminae and muscle fibers destroyed, increased ground substance
		Lung		
				Intima enlarged, irregularities of the elastic fibers, blood between the connective fibers
				Degeneration of the media
+	+	Hemopericardium	Similar to the idiopathic medionecrosis of the aorta	Elastic and muscle fibers destroyed, increased ground substance
	+	Hemopericardium	Rheumatism	
+	+	Hemopericardium		

Table III. *Spontaneous ruptures*

Author	*Age (yr.)*	*Sex*	*Primary disease*	*Localization*	*Aneurysm*
Dlauhy, 1846 (cited by Posselt[6])	22	M	Mitral stenosis	Main trunk	Saccular
Dowse,[16] 1847	19	F	Rheumatism	Main trunk	+
Duffield,[7] 1882	50	F	Pulmonary emphysema	Left branch	Saccular
Posselt,[6] 1896	45	F	Mitral stenosis	Right branch	–
Stoerch, 1899 (cited by Posselt[6])	20	F	Small aorta, several ectasias of the pulmonary artery	Left branch	–
Loveland,[17] 1901	41	M	Chronic adhesive pericarditis, mitral insufficiency	Right branch	Saccular
Mantovani, 1902 (cited by Boyd[18])	25	M	Mitral stenosis, congenital pulmonary stenosis	Main trunk	Spindle shaped
Posselt,[6] 1909	45	F	Mitral stenosis and insufficiency	Right branch	
Arrilago,[19] 1924	38	M		Main trunk	Saccular
Moench,[20] 1924	42	F	Bicuspid pulmonary valve, patent ductus arteriosus	Main trunk	+
Favorite,[21] 1934	18	M	Subtype of cor biatrium triloculare with hypoplasia and dextroposition of aorta	Main trunk	–
Fowler,[22] 1936	59	M		Main trunk	
Dupérie and Lachaud,[23] 1939	44	F	Congestive heart failure, pulmonary atherosclerosis, atherosclerosis	Main trunk	Spindle shaped
Longland,[24] 1943	68	M	Atherosclerosis, atherosclerotic nephrosclerosis	Main trunk	–
Yuski,[25] 1943	21	F	Patent ductus arteriosus	Right branch	Saccular
Hartwell and Tilden,[26] 1943	12	F	Patent ductus arteriosus, subacute staphylococcic endocarditis	Main trunk	Saccular
Deterling,[27] 1947	37	M	Patent ductus arteriosus	Right branch	+
Lindert,[28] 1950	67	F	Patent ductus arteriosus, dissecting aneurysm of aorta	Left branch	–
Ohela and Teir,[30] 1954 (cited by Brettell[14])	72	F			
Thomas, et al.,[29] 1955	42	F	Mitral stenosis	Main trunk	–
Madeloff, 1956 (cited by Brettell[14])	56	F	Mitral stenosis	Main trunk	

Atherosclerosis	*RVH*	*External rupture*	*Interpretation*	*Microscopic findings*
+	+	Hemopericardium		
+	+	Hemopericardium		
+	+	Hemopericardium		
+	+	−		
+		Bronchus	Chronic deforming inflammation	
+		Hemothorax		
		+	Rheumatism, congenital abnormality	
+		−		
+		Hemopericardium	Atherosclerosis	
		Hemopericardium		
		Hemopericardium	Pulmonary hypertension	Elastic laminae farther apart and fragmented
		+		
+	+	Hemopericardium	Atherosclerosis	
		Hemopericardium	Hypoplasia	Picnotic nuclei
		Bronchus	Congenital abnormality	
		−	Congenital abnormality, bacterial infection	
+	+	−	Atherosclerosis, patent ductus arteriosus, trauma	
		Anterior mediastinum		
				Intimal thickening, irregularities of elastic fibers, blood between connective fibers
+	+	Hemopericardium	Pulmonary hypertension	Elastic laminae destroyed, increased ground substance, thickening of intima and adventitia, sclerosis of vasa vasorum
+				Without degeneration of media

Table III. *Spontaneous ruptures*—Cont'd

Author	*Age (yr.)*	*Sex*	*Primary disease*	*Localization*	*Aneurysm*
Kodolova, 1956 (cited by Brettell[14])	40	M	Mitral stenosis	Left branch	
Condry,[32] 1958	61	M	Pulmonary emphysema	Main trunk	–
Brettell,[14] 1960	66	F	Pulmonary hypertension due to thrombosis and embolism	Main trunk	–
	60	F	Pulmonary hypertension (asthma)	Main trunk	–
Ravin, 1960 (cited by Brettell[14])	27	M	Idiopathic pulmonary hypertension	Main trunk, left and right branches	+
Levy, 1960	27	F	Mitral stenosis	Main trunk, right branch	—

Table IV. *External rupture of aneurysms*

Ruptured into	*Number of cases*
Pericardium	18
Mediastinum	2
Bronchus	2
Pleura	1
Lung	1

Table V. *Primary disease in cases of medionecrosis of pulmonary artery*

Primary disease	*Number of cases*
Congenital pulmonary hypertension:	
Patent ductus arteriosus	6
Mitral stenosis	2
Interauricular septal defect	1
Pulmonary stenosis	1
Patent ductus arteriosus, bicuspid pulmonary valve	1
Subtype of cor triloculare	1
Common truncus arteriosus, with 3 valves, interventricular septal defect, hypoplasia of aorta	1
Acquired pulmonary hypertension:	
Mitral stenosis	10
Pulmonary tuberculosis	2
Emphysema	1
Thrombosis and embolism	1
Asthma	1
Without known cause	3

exist in cases of acquired pulmonary hypertension. However, considering the experimental results (medionecrosis caused experimentally in rabbits by collapse) and data from human pathology (medionecrosis of the human aorta after shock) (Faria[38-40]), one is led to think that lack of oxygen may be an important factor. The deficient supply of oxygen may be brought about indirectly by pulmonary hypertension and may be responsible—at least, in part—for the medionecrosis, since obstruction of the vasa vasorum, mentioned by some authors as a cause of medionecrosis of the aorta,[41-45] is in fact not a constant finding.[1,2,3,46-50]

We hope that systematic studies of the pulmonary artery carried out in future research will provide evidence for our theory.

Summary

There are macroscopic and microscopic aspects of medionecrosis of the pulmonary artery which are in line with those described for medionecrosis of the aorta.

Fifteen cases of dissecting aneurysms and 27 cases of spontaneous rupture of the pulmonary artery have been considered, including one case observed by the author. This case had certain peculiarities which had not been described before—partial rupture of the trunk of the pulmonary artery with severe medionecrosis occurring

Atherosclerosis	*RVH*	*External rupture*	*Interpretation*	*Microscopic findings*
				Degeneration of media, elastic fibers fragmented
+	+	Hemopericardium	Atherosclerosis	
+	+	Hemopericardium	Pulmonary hypertension	Increased basophilic substance, connective fibers of media fragmented
+	+	Hemopericardium	Pulmonary hypertension	Increased basophilic substance
		+		Hyalinization of the intima, local destruction of elastic fibers, necrosis at the rupture
+	+	−	Anoxia	Destruction of elastic and muscles fibers, increased ground substance, thickening of intima and adventitia

in a case of mitral stenosis. The patient died during surgical intervention.

The etiology and pathogenesis of medionecrosis of the pulmonary artery are discussed. The importance of pulmonary hypertension and lack of oxygen are pointed out.

Medionecrosis is considered to be an aortic disease of the arteries, affecting vessels of the pulmonary and aortic circulation.

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Initial myocardial infarction among veterans
Nontransmural myocardial infarction
Bundle branch block

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In a previous study[1] of initial myocardial infarction a group of patients was described whose electrocardiograms were typical of transmural infarction. There was an additional group of patients who were treated for their first myocardial infarction but who did not have diagnostic electrocardiographic changes. The electrocardiograms of these patients showed either bundle branch block or only S-T-segment and T-wave changes compatible with a nontransmural myocardial infarction. These patients are reported separately because they represent a poorly defined entity about which less is known.

Selection of study cases

Review was made of records of men discharged with the diagnosis of coronary artery disease from 33 large teaching Veterans Administration Hospitals during the years 1950 to 1952. The records of 631 patients who had had a first myocardial infarction were selected. The details of the sampling technique and criteria of selection were reported in a previous publication.[1]

The 631 cases were subdivided into three groups on the basis of the electrocardiographic findings: (1) transmural infarction—512 cases, or 81 per cent; (2) nontransmural infarction—96 cases, or 15 per cent; and (3) persistent bundle branch block—23 cases, or 4 per cent of the total acceptable group. The transmural group was analyzed and reported on in a previous paper.[1]

Nontransmural myocardial infarction

Two of the original 96 cases of nontransmural infarction were discarded from the study because further review of the electrocardiograms revealed significant Q waves. The electrocardiograms in the other 94 cases were not pathognomonic of an acute myocardial infarction. The clinical picture together with such evidences of myocardial necrosis as fever, elevated erythrocyte sedimentation rate, leukocytosis, and serial electrocardiographic changes were used in establishing the diagnosis.

Description of clinical findings and comparison with transmural group

Age. The age distribution was determined by the method of selection.[1] Twenty-nine (30 per cent) of the 94 patients were under 50 years of age at the time of onset of their

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Received for publication Dec. 30, 1960.

myocardial infarction, and 65 (70 per cent) were 50 years or older. Table I compares the age distribution with that of the previously reported group with transmural myocardial infarction.

History of hypertension and angina pectoris. There was a history of hypertension in 31 per cent of the patients of this group as compared to only 19 per cent in the transmural group (Table I). A history of angina pectoris was found in approximately the same percentage of patients as in the group with transmural infarction.

History of pain. Eighty-nine patients had an episode of pain characteristic of myocardial infarction. The other 5 patients had frequent intermittent episodes of pain. The duration of pain is shown in Table I. The incidence of hemorrhage, shock, vigorous exertion, or operation in the immediate preinfarction period was the same in both groups.

Electrocardiographic findings. Re-examination of the electrocardiograms for the purpose of detailed analysis of the S-T segment and T waves was possible in all but one of this group. All had electrocardiograms showing abnormalities of either the S-T segment or T wave, or both; none showed abnormal Q waves. Six patients had a single electrocardiogram; 5 of these died during the hospital period. In all of the other patients, either T-wave abnormalities or S-T-segment abnormalities, or both, were present in more than one tracing. The electrocardiograms of 2 patients showed only S-T-segment deviations. One of these patients died on the second hospital day and had only one electrocardiogram. The other patient exhibited S-T-segment abnormalities in multiple leads in several tracings. T-wave abnormalities without associated abnormal S-T segments were seen in the electrocardiograms of 13 patients.

Clinical course and laboratory findings. The clinical course and laboratory findings in the two groups differed in certain categories (Table I). There was a higher incidence of shock and leukocytosis in the transmural group. Only 2 per cent of the patients in the nontransmural group had an oral temperature of greater than 101°F. for 3 days or more during the first week, as compared to 10 per cent of the patients in the transmural group. There was no significant difference in the incidence of abnormal rhythms nor of congestive heart failure in the two groups.

There were two definite instances and one questionable one of thromboembolic complications. Eleven patients developed typical electrocardiographic evidence of transmural myocardial infarctions during the hospital period. These electrocardiographic changes represented either a second myocardial infarction or a definite extension of the original nontransmural infarction. In each of the 11 patients there was an associated clinical event characterized by some or all of the following: recurrent episode of pain, shock, fever, leukocytosis, or increase in the erythrocyte sedimentation rate. These transmural infarctions occurred during the first week after the original event in 3 patients, during the second week in 4 patients, and during the third week or later in 4 patients. Three of the 11 patients who developed a transmural infarction died during the first 2 months.

Anticoagulant therapy. Sixty-five (69 per cent) of the patients received anticoagulant therapy, but in 6 patients the dosage used or the duration of therapy was inadequate for any therapeutic benefit. Seven of the 11 patients who developed a transmural infarction were receiving anticoagulant therapy at the time of the event. The 2 patients with a definite thromboembolic complication had not received anticoagulant therapy. Three patients had minor episodes of hemorrhage; one of these had not received anticoagulant therapy.

Immediate and five-year mortality

The integrated records system of the Veterans Administration provided survival data on all patients, without direct communication with a veteran or his family. The deaths during the first 2 months after onset of the acute myocardial infarction are referred to as the "immediate fatalities." Those patients who did not die during the first 2 months are referred to as "survivors" or "recovered patients."

Twelve (13 per cent) of the 94 patients died during the initial 2-month period. Of these 12 patients, 7 died during the first week, 3 during the second week, and one each in the third and fourth weeks. Twenty-one (26 per cent) of the 82 survi-

Table I. *Comparison of nontransmural group with previously reported transmural group*

	94 Nontransmural		*503 Transmural*
	Total number	*Per cent*	*(per cent)*
Age:			
Under 40	7	8	15
40–49	22	23	21
50–59	44	47	42
60–69	18	19	17
70 or over	3	3	5
Interval between onset and admission:			
In hospital	4	4	3
Less than 24 hr.	66	70	62
25–48 hr.	13	14	17
49–72 hr.	6	7	9
73–96 hr.	5	5	9
History of hypertension:			
No	53	56	69
Yes	29	31	19
Unknown	12	13	12
Angina pectoris and duration:			
No	29	31	35
Unknown	7	7	5
Yes	58	62	60
Less than 1 mo.	22	38	50
1–12 mo.	13	22	24
1–4 yr.	16	28	14
5 yr. and over	7	12	11

vors died within 5 years. This ratio is referred to as the 5-year mortality rate among recovered patients.

This present group of patients had a prognosis similar to that of the previously reported transmural group. The differences in immediate mortality rates and in the 5-year mortality rates of survivors of the two groups are not statistically significant (Table II). Fig. 1 illustrates the 5-year survival curves of patients over 50 years of age in each group.

Table III presents comparisons between the expected and the observed annual mortality rates for the survivors in the two groups. The expected annual mortality rates are based upon the 1953 life tables for the white male population of the United States. The difference between the expected and observed annual mortality rates is expressed as the excess mortality rate per annum. The excess mortality rate of patients over 50 years of age was similar in both groups.

The number of patients in this study is too small for detailed analysis of the influence of the individual factors in the past history and clinical course on the mortality rates. Twenty patients did not have shock, temperature of 99.5°F. or more, erythrocyte sedimentation rate of 20 mm. per hour or more, or leukocytosis of 15,000 c.ml. or more during the first week. In spite of the lack of any of the commonly used criteria of myocardial necrosis, the prognosis in this group did not differ significantly from that in the remainder of the study group. Two patients of this group died; one on the day of onset and the other on the nineteenth day after onset of infarction. Four of the 18 survivors died in the next 5 years.

Table I. *Comparison of nontransmural with transmural group*—Cont'd

	94 Nontransmural		*503 Transmural*
	Total number	*Per cent*	*(per cent)*
Hemorrhage, shock, vigorous exertion, or operation prior to onset:			
No	86	92	93
Yes	8	8	7
Duration of pain (of infarct):			
Not specified	22	24	15
Less than 6 hr.	39	41	35
6 hr. or longer	33	35	50
Shock (systolic pressure of 90 mm. Hg or below):			
No	89	95	87
Yes	5	5	13
Digitalis therapy:			
No	84	89	83
Yes	9	10	17
Questionable	1	1	0
Presence of leukocytosis in first week:			
Less than 15,000	72	77	64
15,000 or more	19	20	32
Not recorded	3	3	4
Significant arrhythmias:			
No	86	91	88
Yes	8	9	12

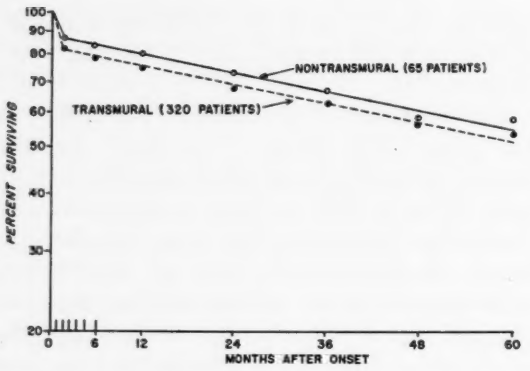

Fig. *1.* Comparison of survivorship in patients with transmural and nontransmural infarction, 50 years of age and over.

Autopsy findings in patients dying with nontransmural infarction

Autopsy protocols were available on 8 of the 12 patients who died during the first 2 months and on 7 patients who died during subsequent hospitalizations. The coronary arteries were not described in one protocol. Severe coronary artery sclerosis with or without occlusion was described in all others. The gross and microscopic appearance in each autopsy corresponded well with the clinical age of the infarction. Neither hemopericardium nor myocardial rupture was found. No evidence of thromboembolic complications was reported in the autopsy findings. A brief description of each case follows.

Patients dying during first 2 months.

CASE I. C. S. died on the day of infarction. An area of tan muscle distal to an occlusion of the circumflex branch of the left coronary artery was described. The heart weighed 430 grams.

CASE II. F.P. died on the second day after onset of infarction. Microscopic examination of an area in the posterior wall of the left ventricle showed disintegrating nuclei. The heart weighed 300 grams.

CASE III. H.L. died on the second day after infarction. An area of infarction in the anterior wall was noted, but was not well described as to extent. There were also scattered areas of fibrosis. The heart weighed 450 grams.

CASE IV. J.M. died on the second day after infarction. A small anterior infarction was fairly well described but the extent was not noted. The heart weighed 400 grams.

CASE V. R.C. died on the seventh day after onset of pain. There was no gross description of the infarction, but, on microscopic examination, areas of fibrosis were described but not localized. The heart weighed 450 grams.

CASE VI. A.G. died on the ninth day after infarction. An area of softening near the junction of the anterior wall and septum was described. The heart weighed 500 grams.

CASE VII. W.P. died on the nineteenth day after onset of infarction. A large transmural infarction involving the anterior wall of the left ventricle and septum was found. It was known from the record that this infarction had become transmural during the second week of hospitalization. The heart weighed 500 grams.

CASE VIII. C.W. died on the twenty-seventh day after onset of infarction. An anterior infarction near the septum was present. From the description this appeared to be subepicardial. The heart weighed 480 grams.

Patients dying during a subsequent hospitalization.

CASE I. J.G. died 8 months after his initial myocardial infarction. Scattered areas of fibrosis in the left ventricle were described. The heart weighed 475 grams.

CASE II. W.R. died from carcinoma of the lung about 1 year after his first infarction. An old infarction was well described. This infarction had become transmural in his sixth hospital week, and at autopsy 1 year later a cardiac aneurysm was described. The heart weighed 300 grams.

CASE III. E.L. died from a second myocardial infarction which occurred 1 year after his first infarction. Scarring from an old infarction was described but was not well localized. The heart weighed 500 grams.

CASE IV. J.M. died 3 years after his first infarction. Areas of fibrosis were described but not localized. The heart weighed 400 grams.

CASE V. E.A. died 3 years after his first infarction. An area of old posterior infarction was mentioned but not well described. The heart weighed 550 grams.

CASE VI. P.F. died from carcinoma of the stomach in 1954, about 4 years after his first infarction. Scattered areas of fibrosis in the anterior myocardium were described at autopsy, but the size of these areas was not mentioned in the protocol. The heart weighed 280 grams.

CASE VII. V.F. died from spinal-cord tumor, 7 years after his initial infarction. On microscopic examination an area of fibrous replacement of the myocardium was described, but the extent was not stated. The heart weighed 385 grams.

Discussion

Exact diagnosis of various syndromes associated with ischemia of the myocardium is difficult or impossible in many cases. This is particularly true of those patients in whom cardiac pain is of intermediate or long duration and is unaccompanied by the classic electrocardiographic picture of a transmural myocardial infarction. The term *transmural infarction* is generally used for those cases in which definitely abnormal Q waves develop in association with the other electrocardiographic changes of myocardial infarction.[2]

The patients described in this paper are

in the group in which diagnosis is difficult. A variety of diagnostic terms have been used to describe the cases of this group. Among these are: subendocardial infarction,[2] coronary failure,[3,4] acute coronary insufficiency,[3,4] intermediate coronary syndrome,[3,4] prodromal symptoms in myocardial infarction,[3,4] impending myocardial infarction,[5] intramural myocardial infarction, and nontransmural myocardial infarction.[6] It is obvious from the number of terms used that none has proved to be satisfactory. *Subendocardial infarction* perhaps has received the widest usage for those cases in which there is associated laboratory or clinical evidences of myocardial necrosis. This term is not entirely satisfactory because it implies an accurate anatomic location, which is not supported either by experimentally produced myocardial lesions[7,8] or by autopsy study of naturally occurring myocardial infarctions, [2,3] unless the subendocardial area is defined as all of the heart excluding only the outer one third or subepicardial area. Furthermore, following the classic experiments of Wilson and co-workers,[9] the term *subendocardial infarction* has also been widely used to include cases of myocardial infarction with definitely abnormal QR complexes.

The incidence of laboratory evidence suggestive of myocardial necrosis, the high mortality rate, and the consistency with which anatomic changes were found at

Table II. *Comparison of mortality of nontransmural group with that of previously reported transmural group*

Type of patient	*Number of patients*	*Deaths in first 2 mo.*		*5-year mortality rate among recovered patients*		
		Number	*Immediate fatality rate/100*	*Number of patients*	*Number of deaths*	*Rate/100*
Nontransmural:						
Under 50	29	3	10	26	2	8
50 and over	65	9	14	56	19	34
Transmural:						
Under 50	183	20	11	163	36	22
50 and over	320	56	18	264	97	37

Table III. *Average excess annual mortality rates among recovered patients during 5-year period after initial myocardial infarction, by age group**

Age group	*Observed average annual mortality rate per 100 recovered patients†*				*Expected average annual mortality rate per 100 recovered patients‡*	*Average excess annual mortality rate per 100 recovered patients*	
	Transmural		*Nontransmural*			*Transmural*	*Nontransmural*
40–49	(94§)	4.9	(19§)	1.1	0.7	4.2	0.4
50–59	(182)	7.1	(36)	6.1	1.9	5.2	4.2
60–69	(66)	7.6	(17)	8.2	3.3	4.3	4.9

*Among 82 male veterans who survived for 2 months after onset of an initial nontransmural myocardial infarction, and 427 male veterans who survived for 2 months after onset of an initial transmural myocardial infarction, survivors in the group of those who were under 40 years of age and in the group of those who were 70 or over were omitted from the table.

†The average annual mortality rates are one fifth of the 5-year mortality rate.

‡The rates shown were calculated from the 1953 life table for white males in the continental United States. The average annual probability of dying during a 5-year period was calculated on the assumption that 1953 age-specific death rates prevailed. These calculated rates were then adjusted on the basis of the age distribution of the "recovered" patients in the study.

§ The number in parentheses is the number of "recovered" patients in each age group.

autopsy suggest that the patients described in this report had myocardial infarction. One or more of the laboratory evidences of necrosis was found in 74 (79 per cent) of the patients in this study. It is very likely that all patients might have shown some evidence of myocardial necrosis if more laboratory examinations had been performed and at optimum times after onset of infarction.

Most physicians regard it as particularly important to determine whether myocardial necrosis or only myocardial ischemia is present. Myocardial necrosis is generally believed to indicate a more unfavorable immediate and long-term prognosis and a need for more vigorous therapy, such as prolonged and marked restriction of activity and the use of anticoagulant therapy.[2] The absence of associated findings of myocardial necrosis is generally thought to indicate a good prognosis.

It is the authors' opinion that too much emphasis has been placed on the laboratory findings suggestive of myocardial necrosis. There would appear to be no justification for considering the type of patients described in this paper as having had a mild or benign myocardial infarction.[10,11] Acute mortality rates of 30 per cent have been reported.[12]

The average excess annual mortality rate of recovered patients was 4 to 5 per cent. This is not significantly different from the rate found in the transmural groups and appears to be the mortality pattern for all patients with symptomatic coronary artery disease. The survival curve[13,14] for patients with angina pectoris is very similar to the survival curves for patients selected on the basis of having had their first transmural infarction or first nontransmural infarction.

Bundle branch block

Twenty-three patients were found to have bundle branch block on the first electrocardiogram taken in the hospital and on all subsequent electrocardiograms. Of these, 10 had left bundle branch block and 13 had right bundle branch block. Four patients had only one tracing, 4 had two tracings, and 15 had three or more electrocardiograms. Twelve patients (52 per cent) died within 2 months after onset of their myocardial infarction. Six of the 11 survivors died within 5 years.

The group is too small for detailed analysis. The patients appeared to be older; 87 per cent were over 50 years of age as compared to 68 per cent in the nontransmural group and 64 per cent in the transmural group. Only 2 patients gave a history of previous hypertension, and only 6 patients gave a history of angina pectoris of more than 1 month's duration. The pain with onset of infarction tended to be of longer duration than in either of the other groups. Nine patients developed shock; 8 of these died. There was a higher incidence of congestive failure (35 per cent) than in the nontransmural group (10 per cent) or in the transmural group (17 per cent). Significant arrhythmia was observed in 6 patients, 4 of whom died during hospitalization.

Autopsy findings in cases of persistent bundle branch block

Autopsy protocols were available on 8 patients. All of these patients died within 2 months after the onset of their infarctions. The infarctions in this group were all large, and in every instance seemed to be anatomically transmural, although the autopsy protocol frequently was not specific in this regard. Marked cardiac enlargement was found in all but one case. There were no instances of cardiac rupture or of hemopericardium. The coronary arteries were well described in all protocols. There was complete occlusion of one major artery in every case, and in two hearts both old and new occlusions were described. A brief description of each case follows.

CASE I. H.M. died on the first day of infarction. A huge anterior transmural infarction extended from the apex to the base of the left ventricle. The adjacent septum was also involved. The heart weighed 375 grams.

CASE II. E.D. died 2 days after infarction. There was a huge infarction which measured 8 by 12 cm. in the anterior wall of the left ventricle. The heart weighed 460 grams.

CASE III. J.G. died on the second day after infarction. The anterior infarction extended from the apex to the base, and also involved part of the septum. The heart weighed 460 grams.

CASE IV. J.C.H. died on the second day after infarction. The infarction was anatomically transmural, included the entire circumference of the apex, and extended halfway to the base anteriorly. The heart weighed 600 grams.

CASE V. S.J. died on the third day after infarction. A posterolateral infarction which included the septum was found. The heart weighed 650 grams.

CASE VI. B.S. died on the third day after infarction. Anterior, posterior, and septal infarctions were found. The heart weighed 420 grams.

CASE VII. J.J.H. died on the eleventh day after infarction. There was a large anterior transmural infarction which included part of the septum. The heart weighed 568 grams.

CASE VIII. H.W. died on the fifteenth day after infarction. The protocol stated that the entire left ventricle and part of the septum was infarcted. The heart weighed 510 grams.

Discussion

A striking feature of this group of patients is the extremely high immediate and 5-year mortality. In view of this high mortality it is thought important to review the prognoses for the patients in the transmural and nontransmural groups who had transient bundle branch block. The patients in the transmural group[1] who showed transient bundle branch block had a 50 per cent immediate mortality, and 56 per cent of the survivors died within 5 years. Only one patient in the nontransmural group developed transient bundle branch block, and he died within 2 months after onset of infarction. The poor prognosis of myocardial infarction complicated by bundle branch block has been previously noted.[15,16]

The high mortality rate is not surprising in view of the very large infarctions found at autopsy. Rosenbaum and Levine[16] reported that all of their patients who had bundle branch block with an initial myocardial infarction had a past history of hypertension. Only one of our autopsied patients (J.C.H.) had a past history of hypertension, although cardiac hypertrophy was present in all but one. Regardless of the etiology of the cardiac hypertrophy, it undoubtedly indicates long-standing heart disease. This is probably another contributing factor to the poor prognosis for patients who have bundle branch block in association with initial myocardial infarction.

The prognosis for patients with bundle branch block has been considered to be that of the underlying disease.[17] However, in this series and others[16] the prognosis for patients with acute myocardial infarction who develop bundle branch block has been shown to be much worse than the prognosis for similar patients who do not show this conduction defect.

Summary

1. An analysis and follow-up is presented of 94 patients with initial myocardial infarction whose electrocardiograms did not show abnormal Q waves. The terminology of this variety of ischemic heart disease is discussed, and *nontransmural myocardial infarction* is suggested as the most appropriate term.

2. The acute and long-term prognosis of this group of patients was not significantly different from that of the group with initial transmural myocardial infarction.

3. An additional group of 23 patients with initial myocardial infarction whose electrocardiograms showed persistent bundle branch block was analyzed. The acute and long-term mortality in this group was very high. All of the autopsied cases had a large area of infarction, and all but one showed significant cardiac hypertrophy.

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The infrequent normal electrocardiogram in cardiac pain

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Forty years have passed since an abnormal electrocardiogram was described in cardiac infarction following coronary thrombosis (Pardee,[19] 1920). Subsequently, a special pattern in the limb-lead tracing was identified with the injury when this occupied either an anterior or posterior position in the left ventricle (Parkinson and Bedford[20,21]). Later, the introduction of chest-lead electrocardiography made it possible to tell the situation of the infarct with greater precision, and a comparison of the electrocardiographic and necropsy findings tested the accuracy of this prediction (Whitten[22]; Barnes[1,2]; Lyon[12]; Myers and associates[14-18]). Alongside this improved localization of the myocardial infarct, a study of certain lesser electrocardiographic signs enabled the recognition of small areas of injury within the myocardium resulting from coronary arterial disease in patients subject to cardiac pain (Evans and associates[8,9]).

The need of the moment is to render infallible the diagnosis of chest pain, and to tell decisively whether it is cardiac pain or not. The most painstaking clinical examination cannot accomplish this by itself. It is true that a patient whose description of his pain in regard to its site, its kind, and its response to exercise, rest, and ingestion of trinitrin, conforms to the narrative which custom has decreed as typifying cardiac pain will usually produce an electrocardiogram which endorses its cardiac source. Nonetheless, the tracing in such a patient often proves to be normal, when later and repeated examinations confirm that the pain has its origin elsewhere than in the heart. Moreover, clinical signs of cardiac pain springing from cardiac infarction are notably sparse in the ambulatory patient, so that the story remains objectively unsupported. It is in this circumstance that a sure symbol for cardiac pain is an obvious need. The question that begs an answer is whether this need is met by the electrocardiogram. If this is to be answered in the affirmative, three postulates must be satisfied. Thus, if the electrocardiogram is to stand as the reliable arbiter in deciding the diagnosis between cardiac and noncardiac pain in a patient with an ache in his chest, and in whom physical signs, like triple heart rhythm, are absent, it must be established, first, that exercise does not change a strictly normal resting electrocardiogram into one customarily accepted as abnormal, secondly, that a normal tracing in one with chest pain does not change within a short period into an abnormal one, and, thirdly, that an electrocardiogram which is abnormal from the effects of coronary arterial disease does not recovery wholly with the passage of time.

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Received for publication Jan. 9, 1961.

LEADS	ANTERIOR INFARCTION	LATERAL INFARCTION	POSTERO-INFERIOR (LATERAL) INFARCTION	POSTERO-INFERIOR (MEDIAL) INFARCTION	SEPTAL INFARCTION
I			—	—	-
II	—	—	—	—	-
III	—				-
IIIR	—				-
$CR_{1,2}$	—	—	—	—	
CR_4		—	—	—	-
CR_7	—			—	-

Fig. *1.* The separate designs in *salient cardiac infarction* in accordance with the site of the injury. In the anterior and lateral varieties, significant Q waves may be added.

The purpose of this paper is to describe an investigation in which these postulates were tested in patients in whom chest pain was the presenting symptom.

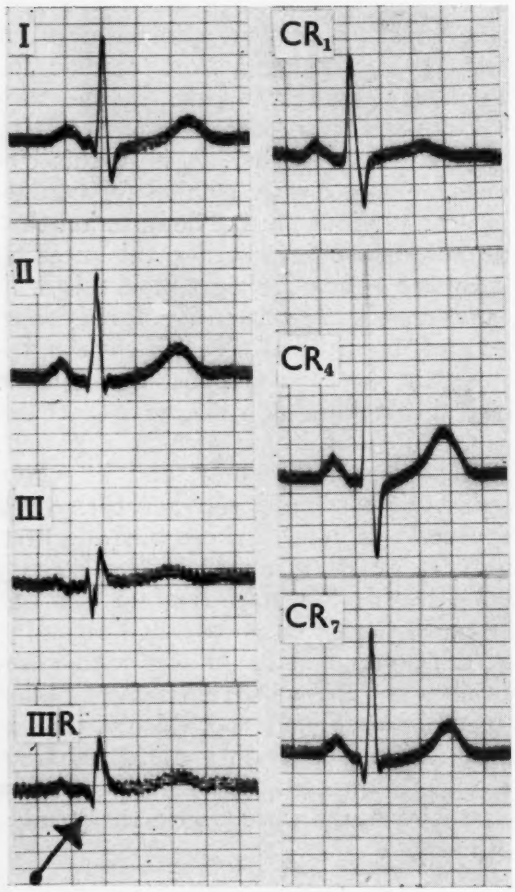

Fig. *2.* Limited cardiac infarction. A Q wave, absent in Lead III, has appeared in Lead IIIR.

We excluded from the study all patients whose cardiac pain arose from either anemia, aortic stenosis, mitral stenosis, or pulmonary hypertension, or was taking place during paroxysms of auricular tachycardia, instances in which the pain arises from causes other than disease of the coronary arteries.

The work has proceeded over a period of 15 years, but, naturally, not all the patients have been observed that long. During this time an attempt has been made to apply an unequivocal diagnosis in every patient and to trace his subsequent progress.

The *electrocardiograms*, numbering some 7,000, have consisted of the bipolar limb leads, I, II, III, and IIIR (Lead III repeated during deep inspiration), and the chest leads, CR_1 and sometimes CR_2, CR_4, and CR_7. The unipolar leads aV_R, aV_L, and aV_F were often recorded, but not once did they give information which had not been provided by the standard bipolar leads. The chest V leads were also frequently recorded, but since they proved to be manifestly inferior to CR leads in the portrayal of the significant lesser electrocardiographic changes, they were not subsequently taken routinely.

The electrocardiogram in healthy subjects after exercise

In that an exercise electrocardiogram was habitually recorded in those patients who suffered from chest pain which in every way was reminiscent of cardiac pain, but

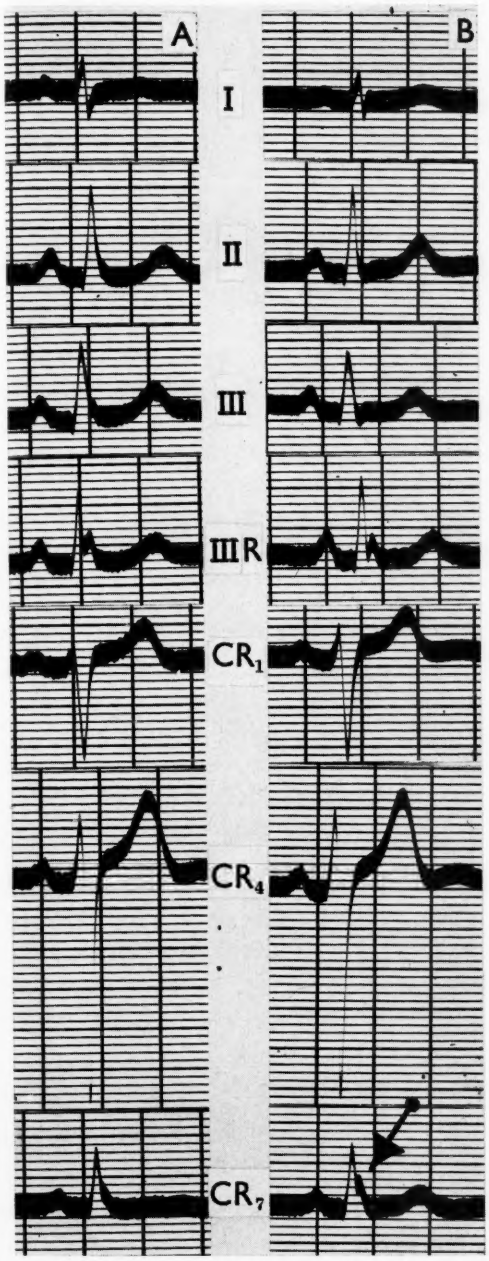

Fig. 3. Limited cardiac infarction. A flat T wave in Leads I and CR_7 in *A* has recovered in *B*, where a notch in RS_7 is the only deformity in the electrocardiogram.

in whom the resting electrocardiogram proved to be a normal tracing, it was a prerequisite that the physiologic changes after exercise in a healthy subject should be known, and that a statutory pattern, accepted as proof of myocardial inadequacy, be established. Such an investigation was carried out by one of us (Lloyd-Thomas[10]). He found that in no healthy subject did strenuous exercise produce changes in the electrocardiogram other than what he regarded as physiologic ones. Thus, provided the R wave was not tall and exceeding 20 mm., a sickle depression, meaning a lowering of the early part of the S-T segment to 1 mm. below the level of the P-Q segment, did not happen, nor did a plane depression, a term applied when the S-T remains flat for a measured interval of 0.1 second before the tracing rises to form the ascending limb of the T wave, nor did the S-T descend below the J at any time during its course; a previously upright T wave never became flat or inverted; the T-U segment was never depressed below the level of the P-Q segment; the U wave was never inverted.

Combined clinical and electrocardiographic classification

Patients with chest pain who were examined consecutively through the years were separated into four groups according to the electrocardiographic findings. Thus, the *first* group comprised those patients with cardiac pain whose electrocardiogram told of salient cardiac infarction. Those in the *second* group suffered from cardiac

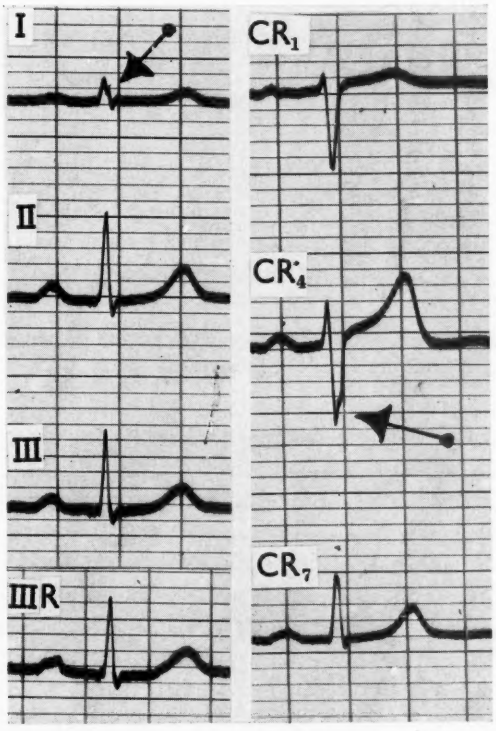

Fig. 4. Limited cardiac infarction. A notch in the RS segment in Leads I and CR_4 is the only abnormality in the tracing.

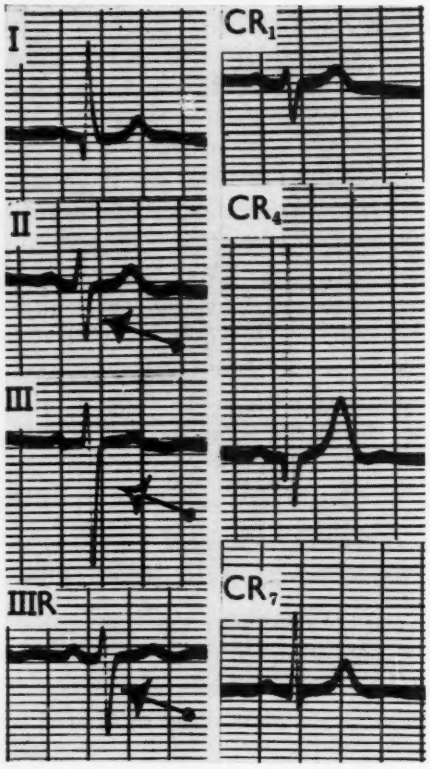

Fig. 5. Limited cardiac infarction. Deep S waves in Leads II, III, and IIIR in the absence of an S wave n Lead I.

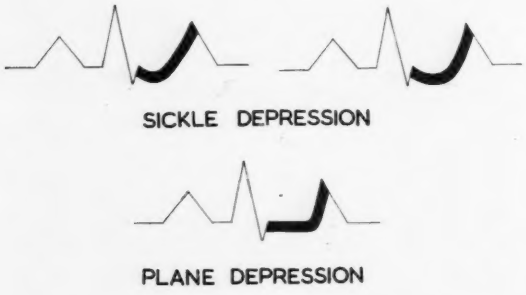

Fig. 6. Schematic representation of significant depression of the S-T segment.

pain, and their electrocardiograms provided evidence of a more limited infarct. In a *third* group were patients with cardiac pain whose electrocardiogram proved to be normal at one time and abnormal another time. Patients in the *fourth* group had chest pain historically reminiscent of cardiac pain, but their electrocardiograms remained persistently normal.

This paper is primarily concerned with he last two groups, but emphasis is given t o the lesser electrocardiographic signs ex- t hi bited by patients who comprised the second group, for a recognition of these has an importance unmatched by any other subject in this field. Only a brief account is given of the first group.

Group I. Cardiac pain; electrocardiogram of salient cardiac infarction. Frank inversion of the T wave in one of more leads, sometimes accompanied by significant Q waves, is the most usual change in the electrocardiogram of patients presenting with cardiac pain. The combination of leads which exhibit such irregularities depends on the location of the infarct, and five electrocardiographic designs have been described as identifying the affected area (Evans[7]) (Fig. 1). Accordingly, infarction of the anterior, lateral, posteroinferior and lateral, posteroinferior and medial, and septal areas of the left ventricle are identified, respectively, by the electrocardiographic designs of T_IT_4, T_IT_7, $T_{III}T_7$, QT_{III}, and Q_1, or bundle branch block, where Roman figures are used to designate limb leads, and Arabic figures the chest leads. Naturally, on occasion, the area traversed by a particular infarct may extend to involve a neighboring sector.

About half of the 2,500 patients with cardiac pain showed one of these designs, and when these were followed up through the years, no electrocardiogram was found to have recovered wholly, although many

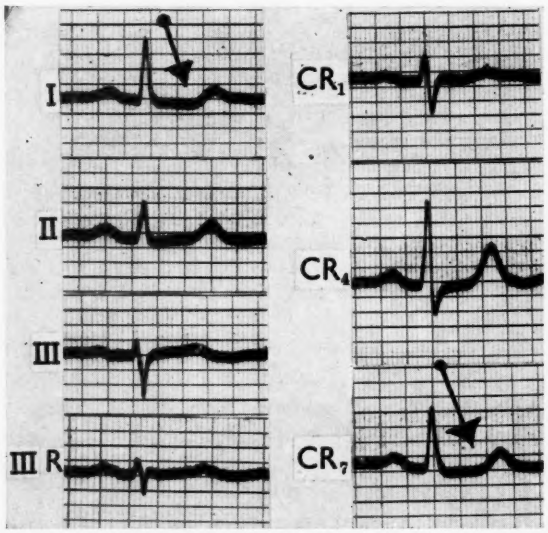

Fig. 7. Limited cardiac infarction. Plane depression of the S-T segment in Leads I and CR_7 from a patient who died 4 days later from extension of the infarct.

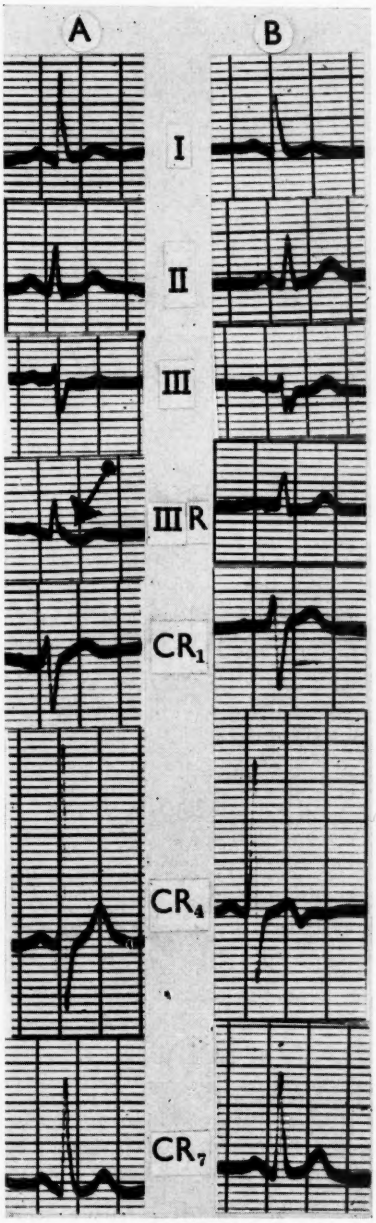

Fig. *8*. Limited cardiac infarction. Sickle depression in Lead IIIR is the only deformity in *A*, recorded 4 years before the extended infarct shown in *B* had taken place.

recovered partially, leaving behind residual changes usually associated with a more limited infarction, a subject to be discussed in the next section.

Group II. Cardiac pain; electrocardiogram of limited cardiac infarction. The patients included in this group also form some one half of the 2,500 patients presenting with cardiac pain. Each showed electrocardiographic deformities which have been classed as lesser changes (Evans and McRae[8]), and which indicated at the time a more restricted or limited kind of cardiac infarction. Although less discernible than those found in salient cardiac infarction, the changes have an equal significance as evidence of coronary arterial disease with its unpredictable course. Indeed, many of the patients exhibiting them showed, after the passage of time, varying from hours to years, the more obvious changes associated with salient infarction. In this way their identification with a myocardial injury from the start was confirmed. Moreover, whenever an exercise electrocardiogram was recorded, the existing changes often became exaggerated and other more obvious deformities might be brought to their side. Although these specific irregularities are sometimes found in the electrocardiograms of noncomplaining older adults, when their significance was being tested, it was held conditional that they should not appear in the tracings of healthy young adults.

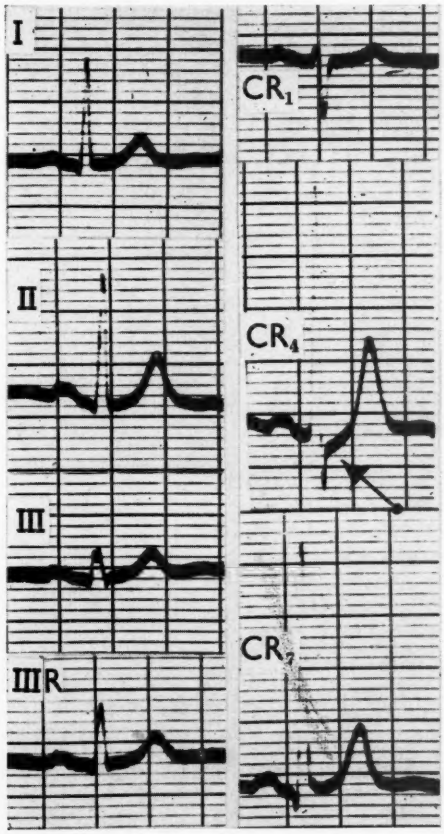

Fig. *9*. Limited cardiac infarction. Sickle depression of the S-T segment in Lead CR_4 is the only deformity in the tracing from a patient with cardiac pain.

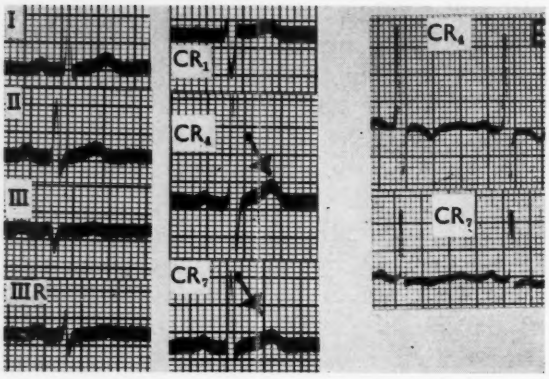

Fig. *10.* Limited cardiac infarction. A low T wave in Leads CR_4 and CR_7 (*arrows*) became inverted after exercise (*E*).

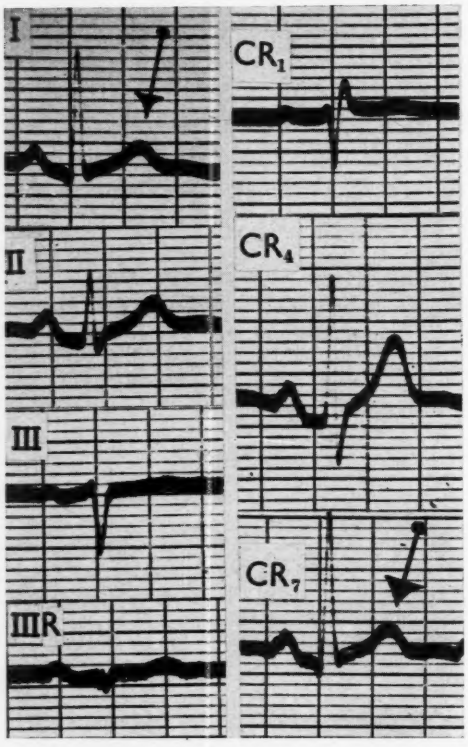

Fig. *11.* Limited cardiac infarction. A blunt T wave in Leads I and CR_7 is the only deformity in the tracing from a patient with cardiac pain who died 2 months later from extension of the infarction.

Experience has confirmed the need to seek these more cryptic signs methodically in seven sectors of the single-beat complex; they concern the Q wave, the RS limb, the S wave, the S-T segment, the T wave, the T-U segment, and the U wave.

THE DISTRIBUTION OF NATURAL Q WAVES.

Q in IIIR: By a natural Q wave we mean one not more than 3 mm. in depth nor wider than 0.04 second. When a small Q wave, absent in the limb lead III, appears in IIIR, it is unequivocal evidence of a myocardial fault (Fig. 2). The sign does not appear in healthy subjects, and the lead-combination III and aV_F does not always find it, confirming the indispensability of IIIR in the investigation of any patient with chest pain.

In extrasystoles: Occasionally, and in the absence of significant changes in the remainder of the electrocardiogram, the appearance of a natural or larger Q wave in a fortuitously recorded ventricular extrasystole in leads other than Lead III has given confirmation of the cardiac source of chest pain.

In odd leads: The incidence of a natural Q wave in electrocardiograms from healthy subjects and from patients with cardiac pain led Evans and Pillay[9] to conclude that its presence in single leads or in a combination of leads (listed in Table I) provided evidence of a myocardial injury. The present study has confirmed this view, but it has also emphasized the relative infrequency of the electrocardiographic anomaly as a lone sign of a myocardial fault.

THE RS LIMB. Notching of the QRS in diverse leads is a common finding in the electrocardiogram of healthy subjects, but its presence in CR_7, even by itself, is evidence of a myocardial injury (Fig. 3). Again, its presence in I and CR_4 is similarly a significant, but rare, sign (Fig. 4).

THE S WAVE. An S wave greater than the R wave in the limb leads II and III, in the absence of an S wave in Lead I, has been

Table I. *Single leads or combination of leads that did not show a Q wave in 500 symptomless and apparently healthy subjects*

Number of leads in combination	*Leads specified*
Single lead	I. II. IIIR. CR_4.
Two leads	I and II. I and CR_4. II and CR_4. CR_4 and CR_7.
Three leads	I, III, and IIIR. I, II, and CR_4. II, CR_4, and CR_7. III, IIIR, and CR_4.
Four leads	I, II, III, and IIIR. I, III, IIIR, and CR_4. I, III, IIIR, and CR_7. II, III, IIIR, and CR_4. III, IIIR, CR_4, and CR_7.
Five leads	I, II, III, IIIR, and CR_4. I, III, IIIR, CR_4, and CR_7.

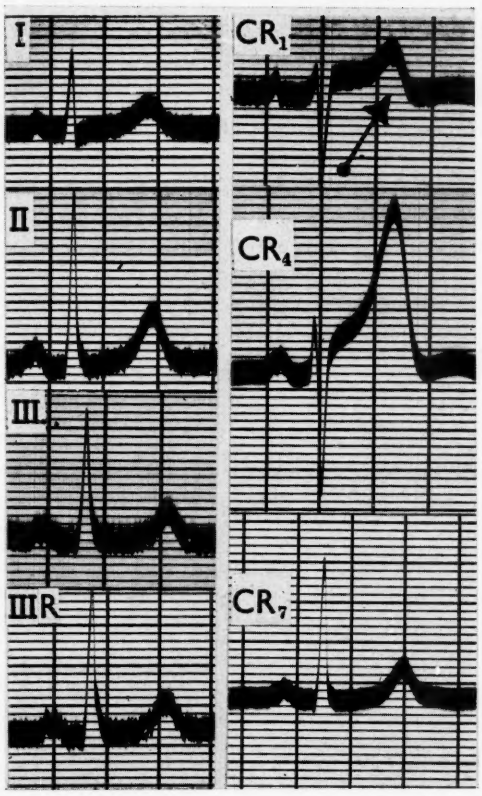

Fig. *12.* Limited cardiac infarction. A sharp descent of the T wave in Lead CR_1 (*arrow*) is the only abnormal sign in the electrocardiogram of a patient with cardiac pain. A subsequent tracing was grossly abnormal.

shown to indicate a lesion in the anterolateral portion of the left ventricle (Wilson and associates[23,24]; Duchosal and Jornod[6]; Davies and Evans[5]). In a patient with chest pain this sign may be present alone or in company with other lesser or more obvious signs of cardiac infarction (Fig. 5).

THE S-T SEGMENT. A depression of this portion of the electrocardiogram provides a most important sign of an injured myocardium, unless the effect is due to digitalization; the change affects the segment in its proximal or distal portions, producing, respectively, either a *sickle* or *plane* deformity (Figs. 6 and 7). In one third of the cases in our series the deformity was confined to IIIR (Fig. 8), again emphasizing the importance of this lead in the investigation of a patient with chest pain.

Another lead in which depression of the S-T segment supplies a ready clue to the presence of a myocardial fault is CR_4. Thus, in the presence of a moderate S wave, a depression of the early part of the S-T, causing a sickle deformity, wherein the J point is lowered below the level of the P-Q segment, is an abnormality never found in the electrocardiogram of healthy subjects (Fig. 9).

THE T WAVE.

The low and blunt T: A *low T wave* in Leads I and CR_4 or in Leads I and CR_7 cannot by itself be accepted as evidence of a myocardial fault, so that in a patient who exhibits this electrocardiographic sign an exercise electrocardiogram has to be recorded in order to decide whether the pain has a cardiac source or not (Fig. 10).

On the other hand, a *blunt T wave* (Fig. 11) in the resting electrocardiogram

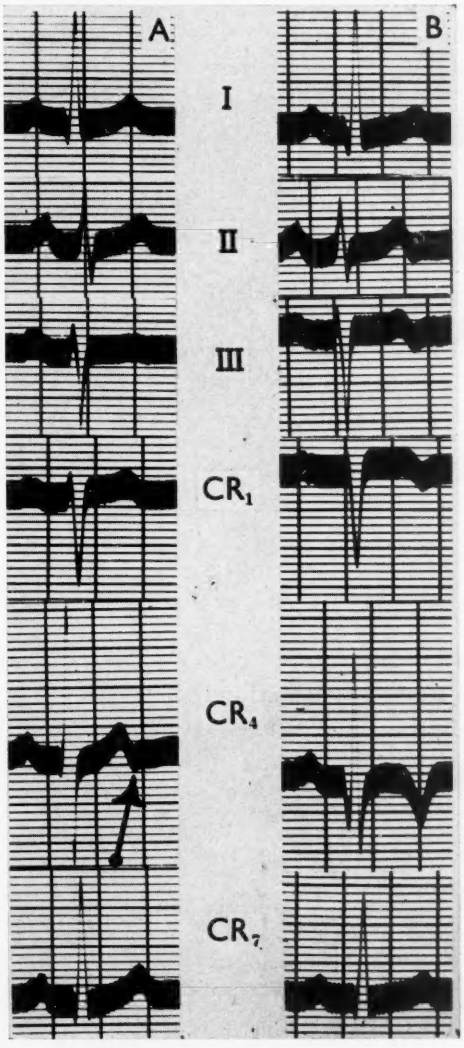

Fig. *13.* Limited cardiac infarction. A terminal dipping in a low T wave in Lead CR_4 is the only deformity in *A*, recorded a few months prior to extension of the infarct shown in *B*.

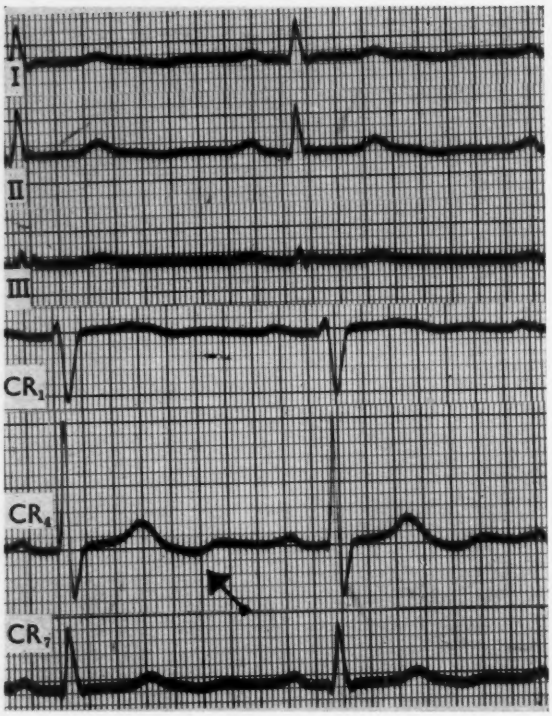

Fig. *14.* Limited cardiac infarction. Depression of the T-U segment in Lead CR_4 associated with inversion of the U wave in Leads I and II.

is pathognomonic of a myocardial lesion, even when the wave has hardly lost height.

Sharp descent of T in the right pectoral lead: This electrocardiographic sign which can by itself identify the cardiac source of a pain is uncommon. The near-vertical drop of the descending limb of the T in Leads CR_1, CR_2, and perhaps CR_3 may be easily appreciated when it is compared with the more gradual decline of the wave in a neighboring lead like CR_4, when simultaneously recorded (Fig. 12).

Terminal dip of T wave: This is a common finding, usually in the apical chest lead, in a patient in whom the onset of cardiac pain has been recent; a deformity of the T in Lead I commonly accompanies this change. It is when it appears as a lone sign, and in an otherwise normal electrocardiogram, that its recognition assumes importance (Fig. 13).

THE T-U SEGMENT. A casual glance at the electrocardiogram of a patient subject to chest pain may fail to notice depression of the T-U as a slight departure of the tracing from the normal, because a lowering of this segment by only half a millimeter below the level of a recognizable U-P segment confirms the presence of a myocardial lesion. So far, we have only found this sign in cardiac infarction (Fig. 14).

THE U WAVE. Inversion of the U wave in a patient with a limited myocardial injury from coronary arterial disease is sometimes its only electrocardiographic sign (Fig. 15). The same deformity can also appear as an early change in left ventricular preponderance from any cause, and in the absence of an added ischemic myocardial lesion.

Group III. Cardiac pain; one-time normal electrocardiogram. In only 46 among 2,500 patients with proved cardiac pain was the electrocardiogram a physiologic tracing at one time and an abnormal record at another time. This relatively small incidence by itself gives emphasis to the importance of the electrocardiogram in deciding whether a patient with chest pain has cardiac pain. Yet, it is large enough to invalidate the test as one which could invariably provide an infallible answer, unless it can be shown

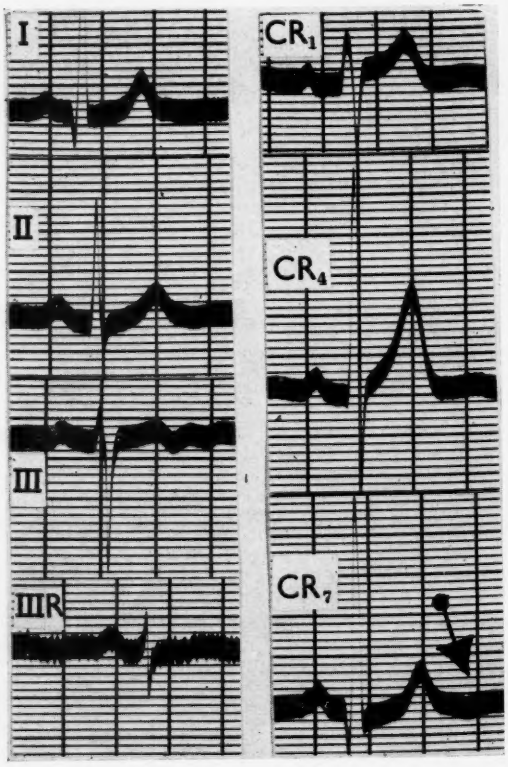

Fig. *15.* Limited cardiac infarction. Inversion of the U wave in Lead CR_7 is the only deformity in the tracing from a patient with proved cardiac pain. Inversion of the T in Lead III is corrected in Lead IIIR.

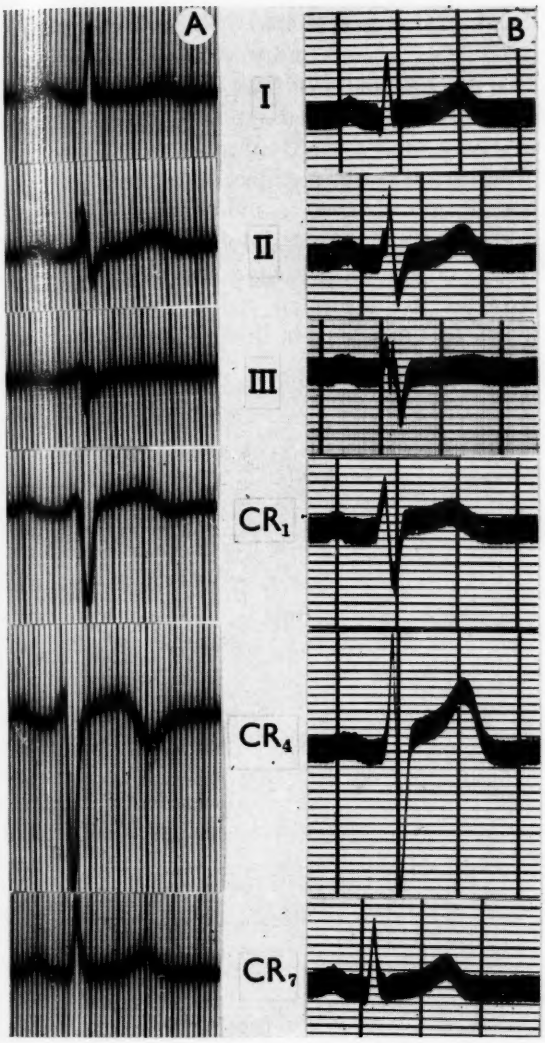

Fig. *16*. The mutable electrocardiogram (Type I) A low T wave in Lead I, inverted T in Lead CR_4, and terminal dipping of the T in Lead CR_1, seen in *A*, are absent in *B*, recorded some time later.

that these 46 patients presented a peculiar type of tracing which labeled them as distinctive and as exhibiting pain which is prognostically less sinister than the one arising from frank cardiac infarction. The changing electrocardiograms recorded in patients forming this group, therefore, came under special scrutiny, and they were found to conform to two types.

THE MUTABLE ELECTROCARDIOGRAM (TYPE I). In 33 of the 46 patients the tracing assumed the pattern described by Evans,[7] in which the T wave was low, and usually inverted, in the limb lead I, and in chest leads reaching from the right pectoral (CR_1) as far as the apical lead (CR_4) and usually beyond (Fig. 16). These changes were distinctive in regard to the specific leads which showed the T-wave deformity and were not accompanied by significant Q waves nor by depression of the S-T segment. If by chance either of these two faults were added, although recovery of the deformed T waves might have taken place, residual changes in some part of the tracing remained as evidence of cardiac infarction, limited though it was to a small area (Fig. 17).

Evans postulated that this mutable electrocardiogram indicated a diffuse and intense cardiac ischemia from interruption of the blood flow in the left coronary artery. The wide distribution of the T-wave inversion suggested that the artery was involved

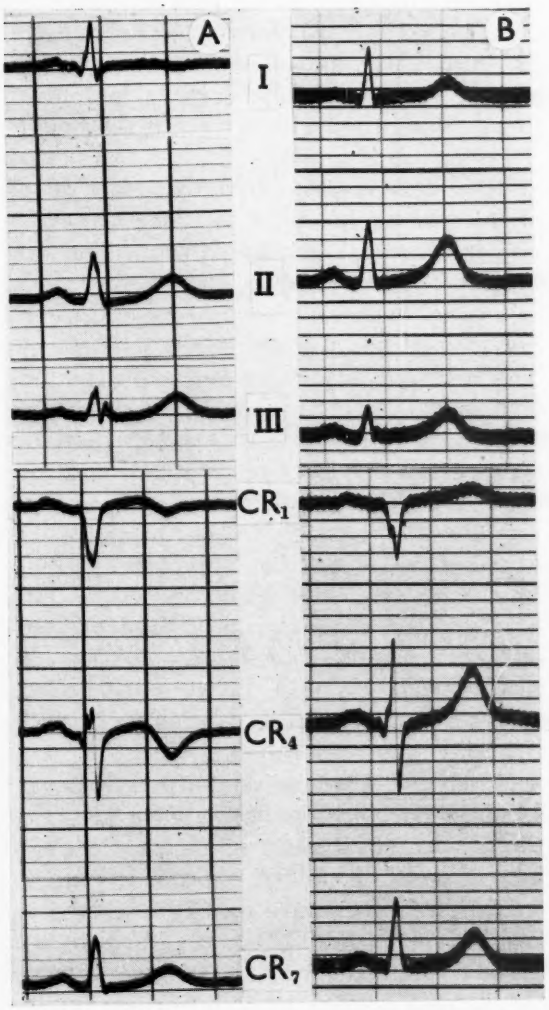

Fig. *17*. Limited cardiac infarction. The tracing *A* simulates *A* in Fig. 16 except for the presence of a Q wave in Lead CR_1, and this abnormality persists in the largely recovered tracing in *B*.

near its source. Such interruption is short-lived and does not last long enough to cause more than a transient heart muscle-cell dysfunction. Within 3 to 6 months, and sometimes sooner, the myocardium regains its electrically normal state when attacks of cardiac pain cease to recur. It is likely that the episode is caused by spasm of the artery unaffected by material atherosclerosis, and it is because of its innocent nature that its recognition is so desirable in the occasional subject presenting it.

THE MUTABLE ELECTROCARDIOGRAM (TYPE II). In the other 13 patients in whom an electrocardiogram which was abnormal at one time was normal at another time, the tracing again assumed a uniform pattern, but different from the previous kind. In this instance, when the tracing was abnormal, the T wave was inverted in Leads III and IIIR and low or sometimes inverted in Lead II, whereas a significant Q wave was absent from these leads and the T was normal in CR_7 (Figs. 18 and 19). In this last respect, therefore, and in its characteristic behavior of reverting to a normal tracing, it differed from the electrocardiogram standing for salient cardiac infarction of the posteroinferior and lateral portions of the left ventricle, wherein the T is inverted in CR_7 as well as in the limb leads.

Although arteriospasm of the kind described for the previous type of mutable electrocardiogram may be operating to produce this tracing, it could have another explanation. Thus, an interruption of a branch of the right coronary artery may have taken place in the presence of an efficient collateral circulation which ensured the survival of those heart muscle fibers subjected to the transient ischemia (Lowe[11]; Blumgart and associates[4]).

Group IV. Cardiac-like pain; persistently normal electrocardiogram. Among 3,546 patients with chest pain which was in every way typical of cardiac pain in regard to its site, its kind, and its relation to rest or exercise, and even sometimes in respect to its relief by trinitrin, the resting electrocardiogram proved to be a normal tracing in some one third of them. Moreover, it remained normal when recorded at subsequent examinations after periods of months or even years, and an exercise electrocardiogram never showed changes indicative of the effects of coronary arterial inadequacy.

In the majority of the patients, functional dyspepsia was considered to be the cause of the pain, so that many gave a history of habitual constipation and excessive flatulence, and showed esophageal arrhythmia during a barium swallow, and a "cup and spill" design of the opaque meal when it entered the stomach, which was bent on itself by much gas in the splenic colon.

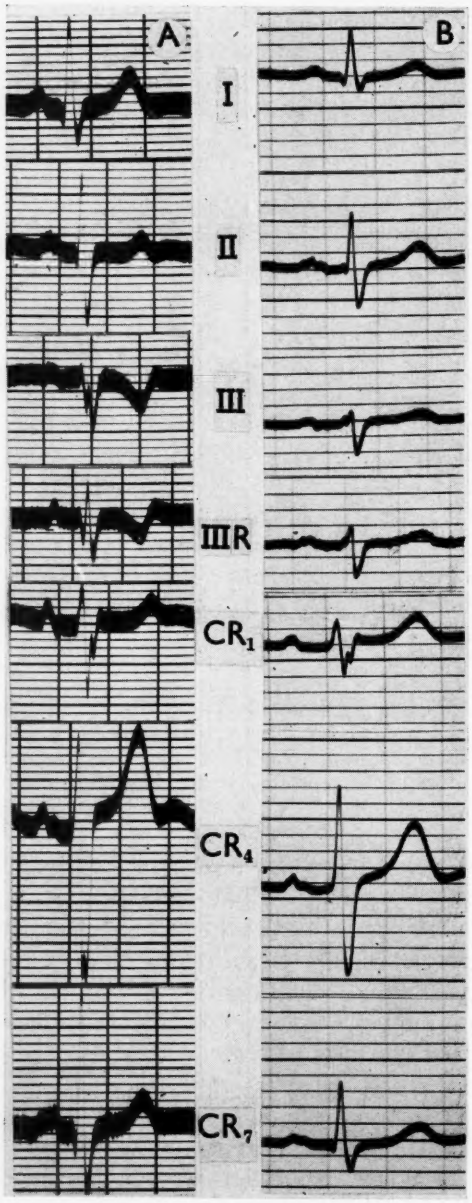

Fig. *18.* The mutable electrocardiogram (Type II). In *A* the T wave is low in Lead II and deeply inverted in Leads III and IIIR. These changes are absent in the normal tracing (*B*) recorded later when the patient was no longer liable to cardiac pain.

Table II. *The extent to which the electrocardiographic deformity was exaggerated after exercise in 20 patients who showed lesser electrocardiographic signs with cardiac pain, and in 20 patients with similar electrocardiographic changes but without pain*

Pain	*Number of patients*	*Extension of positive electrocardiographic changes after exercise*			
		Absent	*Slight*	*Moderate*	*Prominent*
Present	20	0	4	4	12
Absent	20	2	13	5	0

Many lost their symptoms when antidyspeptic measures were introduced or when reassured that nothing ailed the heart, and in none was it necessary at subsequent examinations to retract such reassurance once it had been given on the basis of finding a strictly normal electrocardiogram during a time at which the patient was liable to periodic attacks of pain.

The place of the exercise electrocardiogram in the diagnosis of cardiac pain

In the past the exercise electrocardiogram has proved useful to test the significance of certain small signs in the tracings of patients with cardiac pain recorded at rest. Now that these have become known, the test need only be applied for diagnostic purposes in the case of one of them, namely, when the T wave is low in Lead I and in Leads CR_4 or CR_7, for this change can be present in circumstances other than cardiac pain, and not infrequently in health.

It is known (Biörck[3]; Master[13]) that the exercise test in patients who have contracted cardiac infarction may show fewer abnormalities with the passage of time; presumably this reflects the development of a more adequate collateral circulation, and, so, the exercise electrocardiogram may prove useful in estimating the efficiency of this alternate blood supply. In order to test the validity of this assumption, we compared the extent of the electrocardiographic changes which followed exercise in 20 consecutive patients who showed limited cardiac infarction and cardiac pain, with those in 20 patients who had no chest pain, but in whom a routine electrocardiogram showed changes of limited cardiac infarction like unto the former group (Table II).

In the first group with cardiac pain, an increase in the changes was prominent in 12, moderate in 4, and slight in only 4 (Fig. 20). In the second group without chest pain, exaggeration of the changes was never prom-

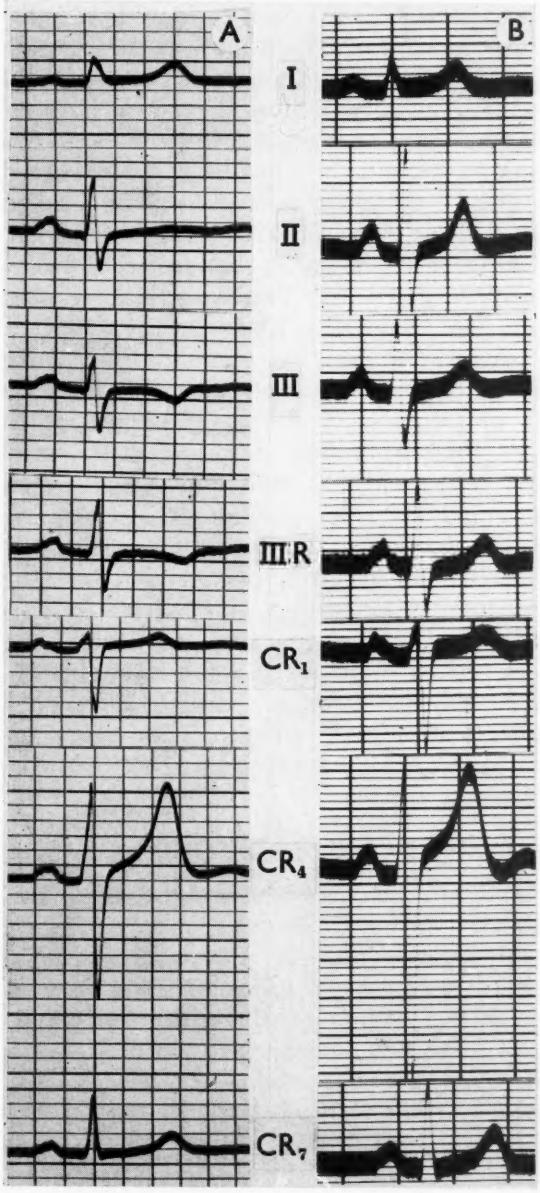

Fig. *19*. The mutable electrocardiogram (Type II). In *A* the T wave is flat in Lead II and inverted in Leads III and IIIR. These changes are absent in the normal tracing (*B*) recorded later when the patient was no longer liable to cardiac pain.

inent; it was moderate in only 5 cases, slight in 13, and absent in 2 cases (Fig. 21). Thus, the exercise electrocardiogram has greatest value in the examination of adults when an obligatory examination has included an electrocardiogram which has uncovered the characteristic signs of limited cardiac infarction, and when the subject, in order to win some advantage, might be suppressing a history of chest pain. This circumstance might arise in the course of an examination for life insurance, or when the examination which has to include electrocardiography is conditional for an election into a superannuation scheme. It would seem to be fair inference that, if the changes in the exercise electrocardiogram are conspicuous, pain on effort is to be expected in most cases on account of the proved inadequacy of the collateral circulation. Conversely, if such changes are inconspicuous, pain may be absent because of an efficient alternative blood supply.

A positive exercise test in the rare cases exhibiting the mutable electrocardiogram is only obtained during a period which immediately follows the return of the tracing to normal, and it is not expected at a later period when the patient is remaining free from chest pain.

In the fourth group of cases, in which the resting electrocardiogram is a strictly normal tracing during a time when recurring paroxysms of chest pain are strongly presumptive of cardiac pain, the exercise electrocardiogram will not show signs indicative of inadequacy of the coronary circulation.

Summary and conclusions

Pain in the chest is a common complaint. Its description in terms of character, place, and spread, and its reaction to exercise or to rest, cannot predict its source with certainty. Moreover, the sparsity of physical signs in a patient with cardiac pain is notable, so that undue reliance on the history frequently misleads in diagnosis. A search, therefore, has been directed to finding a formula which can tell unequivocally whether a pain in the chest arises from the heart or not. It is known that certain abnormalities in the electrocardiogram of one with chest pain have their source in cardiac infarction, but the ability of a normal tracing to exclude cardiac pain has not yet received universal acceptance.

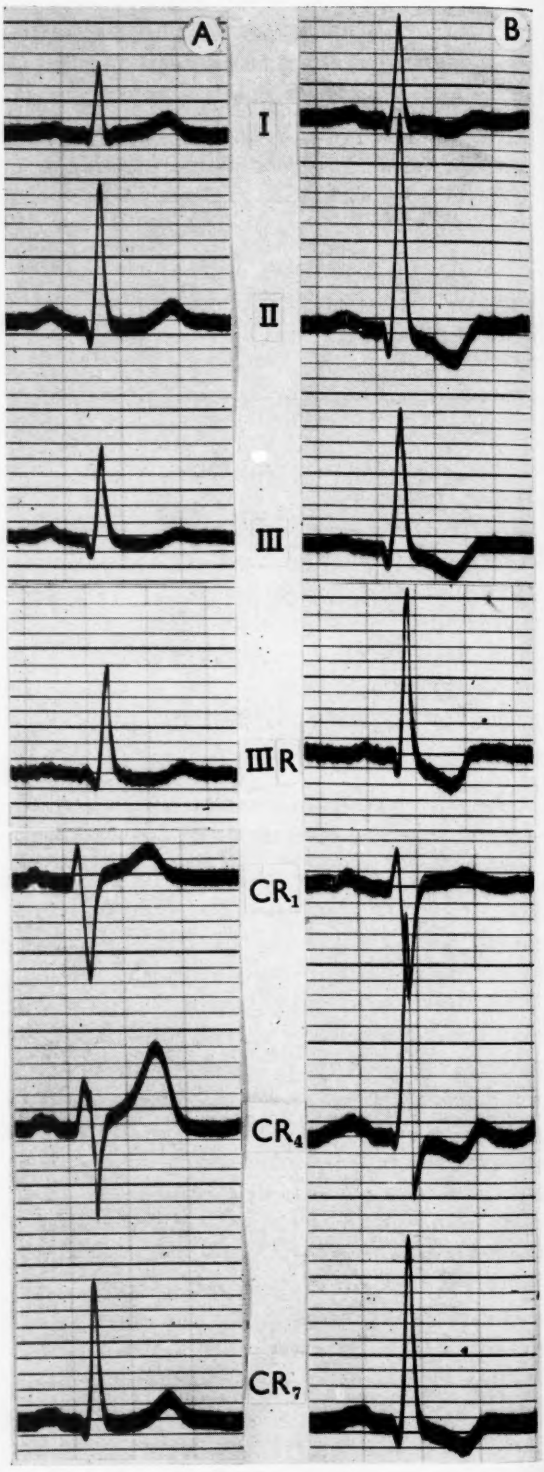

Fig. *20*. The effect of exercise on the electrocardiogram in limited cardiac infarction with chest pain. S-T depression in Leads III and IIIR in the resting electrocardiogram (*A*). After exercise (*B*) there is gross S-T depression in several leads.

The clinical and electrocardiographic supervision over a period of 5 to 15 years of 3,546 patients with chest pain, which was presumed from the history to be cardiac pain, found that they fell into four groups.

Some one third of the patients belonged to the *Group I*, in which the design of the electrocardiogram confirmed the presence of *salient cardiac infarction*. According to the place of the infarct the T wave was inverted in either Leads I or CR_4 or in both (anterior distribution), in Leads I and CR_7 (lateral), in Leads III and CR_7 (posteroinferior and medial). In septal infarction the Q was deep in Lead CR_1 and in leads more to the left, or a bundle branch block was present. A significant Q wave was often present in the first two designs, and in the last four the S-T segment was depressed in Lead IIIR. Naturally, two or more of the designs appeared together when the infarct trespassed on adjoining areas.

Another third of the patients belonged to the *Group II*, in which cardiac pain was associated with lesser electrocardiographic changes, which told of a more *limited cardiac infarction* at the time. Such changes included a natural Q in Lead IIIR when it was absent in Lead III, a notch in RS_7, a deep S wave in Leads II and III when S was absent in Lead I, depression of the early (sickle) or late (plane) portions of the S-T segment in any lead, particularly Lead IIIR, with the exception of Lead III, a low T in Leads I and CR_4 or CR_7, blunt T wave, sharp descent of the descending limb of the T wave in the right pectoral lead, terminal dipping of the T wave, especially in Lead CR_4, depression of the T-U segment, and inversion of the U wave.

Many electrocardiograms in the first group moved in time to resemble those in the second group, and similarly from the second to the first.

Group III comprised only 46 patients with cardiac pain resulting from *temporary ischemia*, in whom the electrocardiogram was abnormal at one time and normal at another time. The mutable electrocardiogram in these cases conformed with one of two designs. In the first, of which there were 33 examples, the T wave was either low or inverted in limb lead I and was inverted in chest leads CR_1 to CR_4 and even beyond. The tracing which showed neither significant Q waves nor depression of the S-T segment recovered completely in time, usually in the course of 3 months. In the second variety of mutable elec-

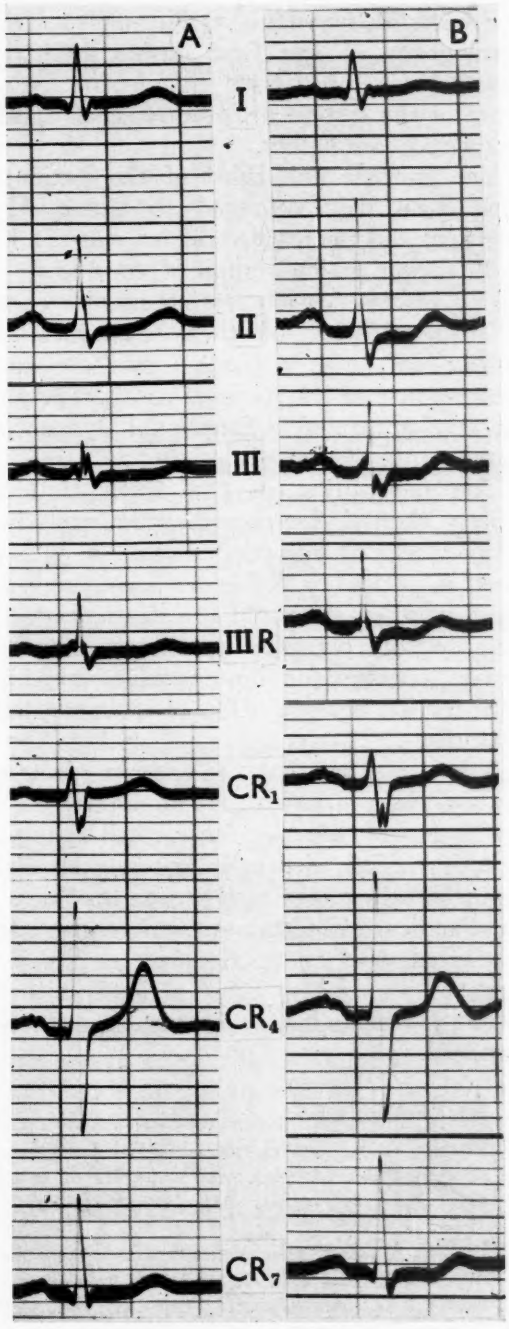

Fig. *21*. The effect of exercise on the electrocardiogram in painless limited cardiac infarction. Depression of the S-T segment in Leads II, III, IIIR, and CR_7 in the resting electrocardiogram (*A*) are only slightly exaggerated in *B*, recorded after exercise.

trocardiogram, of which there were 13 examples, the T wave became inverted in Leads III and IIIR, and low in Lead II, again in the absence of both significant Q waves and S-T depression, and also without lowering of the T wave in Lead CR_7; this last finding differentiates it from posteroinferior cardiac infarction. Three of our patients in whom a mutable electrocardiogram of the first design had recovered developed later the electrocardiogram of the second design, and then again recovered completely.

Yet another one third of the patients with chest pain belonged to *Group IV*, in which the electrocardiogram was a normal tracing which remained so during a period of observation lasting many years. In the majority of these examples of *cardiac-like pain*, a barium swallow and the response of the patients to appropriate therapy confirmed a functional dyspepsia as the cause of the pain.

The recognition of the truth that a strictly normal electrocardiogram excludes cardiac pain if recorded during a period when a patient is liable to paroxysms of chest pain, even should the description of his symptom presume a coronary arterial source, ensures for innumerable subjects a protection against a life of unwarranted invalidism.

It is suggested that the exercise electrocardiogram can play a part in assessing the significance of the lesser electrocardiographic signs identified with coronary arterial disease when they are found during an obligatory medical examination, such as the one connected with an application for life insurance, and when chest pain is either absent or when a history of it is deliberately withheld.

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Experimental and laboratory reports

Movement of the heart during the period between the onset of ventricular excitation and the start of left ventricular ejection

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The present communication is the first of several aimed at a more precise definition of the mechanical sequence of the heart beat. This definition is based on the close agreement between the results of the application of two unrelated indirect techniques to two different species under widely varying experimental conditions. The methods utilized have been extended and improved since the preliminary report of this work.

During the isometric phase of systole there is a continuing increase in the number of fibers which have entered into contraction. Thus, one might expect to observe not only a steady rise in the actual pressure but also a progressive increase in the rate of rise in pressure. However, the latter condition is not fulfilled. Despite the increment in the actual pressure, the *velocity of rise is irregular and "jerky"* in both ventricles (Fig. 1). This has been true not only in all dogs but in numerous human subjects who have been studied at operation or by cardiac catheterization. We think it improbable that these irregularities in the rate of rise in pressure are due to artifacts, because they tend to be constant not only from cycle to cycle but from subject to subject. Furthermore, the directional changes in the velocity curves are often reflected as changes in slope in the conventional pressure records. Indeed, the chief advantage of the former traces is their great detail, in that they show more frequent alterations in direction and may exhibit changes in slope which cannot be detected in the undifferentiated pressures.

The simultaneous study of pressure velocity curves from two adjacent cardiac chambers appears to offer an explanation for this apparent paradox, i.e., the observation that despite the steady increase in the number of contracting fibers the rate of rise in pressure is not smooth but irregular. Thus, as is shown in Fig. 1, there is at times a reciprocal relationship between the velocity curves from the two ventricles; a decreasing rate of rise in one chamber is associated with an increasing rate in the other. This phenomenon, which has been regularly observed, is probably due to motion of the interventricular septum toward one ventricle and away from the other.

Similar reciprocal changes in the pressure velocity curves have been consistently found in the records from the aorta and from the

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Aided by grants from the United States Public Health Service [HTS-5148C(3)], from the American Heart Association, and by gifts from Mr. Horace Hall, Mr. Hugh Kaul, and Mr. L. E. Willson.
Received for publication Dec. 5, 1960.
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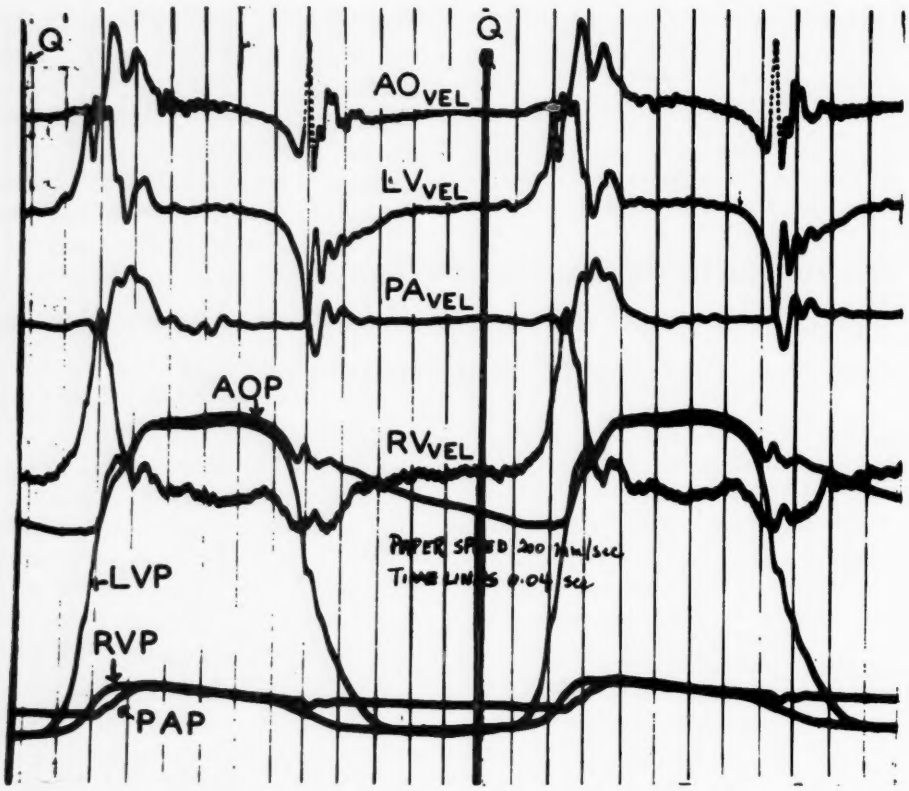

Fig. *1*. The pressure traces from the two ventricles (*LVP*, *RVP*), the aorta (*AOP*), and the pulmonary artery (*PAP*) of a dog are shown. The first time derivative (dP/dt) of these pressure pulses is also illustrated: LV_{vel}, RV_{vel}, AO_{vel}, PA_{vel}. The velocity traces display much more detail than the undifferentiated pressure records from the same chambers.

left ventricle, and are thought to be caused by movement of the semilunar valves either toward the aorta (ballooning because of the higher pressure below) or toward the ventricle (pull on the aortic ring). Reciprocal changes also occur between the right ventricle and the pulmonary artery and between each atrium and the corresponding ventricle. These findings have provided an indirect method of studying the movements of the structures (valves, interventricular septum) which separate the cardiac chambers from each other and from the great vessels. The correlation of such movements with the precordial motions in order to gain an insight into the genesis of the latter is the main objective of this and subsequent reports.

Subjects and methods

Kinetocardiograms were recorded from 41 healthy adults. In 22 of these persons, traces were obtained only from the four areas corresponding to the V_1 to V_4 electrocardiographic points. Nine subjects had similar traces plus records of the heart sounds from the mitral, tricuspid, pulmonic, and aortic areas. The last 10 individuals were deliberately selected from young (19 to 26 years; 3 males and 2 females) and middle-aged (46 to 59 years; 4 males and 1 female) groups. They were studied in more detail; precordial tracings were obtained from the second to the sixth intercostal spaces, inclusive, in vertical lines corresponding to the V_1, V_2, V_4, and V_5 lines. Movements in the V_3 line were not recorded because they are usually similar to those from the V_2 and V_4 areas. Likewise for these 10 subjects, records were obtained from the suprasternal notch and from the right and left epigastric regions.

When the records from these 41 subjects were analyzed, it soon became apparent that those from the 10 persons who were subjected to the "chest mapping" procedure contained more pertinent informa-

tion than could be found in the traces from the other 31 individuals who were studied less intensively. Consequently, the several tabulations presented in this and succeeding reports deal only with the data from these 10 persons. However, the findings in this group are also representive of those in the larger number of subjects.

In 18 open-chest dogs, pressures were recorded from the aorta, pulmonary artery, and from the four cardiac chambers. The curves representing the change in velocity of pressure were obtained by electronic differentiation of the pressure pulses. The recording system consisted of metal cannulae connected to strain gauge transducers (Statham P23Db) of equal sensitivity, and an 8-channel oscilloscopic recorder (Electronics for Medicine). The frequency response of the system was tested by a sine wave pressure generator and appeared to be flat to more than 100 cycles per second. The cannulae were introduced into the cardiac chambers through the respective atrial appendages and into the roots of the great vessels through appropriate branches. The position of all cannulae were verified at autopsy.

Because of experimental difficulties, simultaneous tracings from all adjacent areas were not always secured. In the analysis of the data, only technically satisfactory records were studied.

Explanation of terms. The kinetocardiographic (KCG) areas are designated as in previous publications. The first subscript to letter K refers to the vertical V lines, as used in electrocardiographic terminology, whereas the second subscript indicates the intercostal space. Thus, K_{13}, K_{45}, and K_{54} refer, respectively, to records obtained from the right parasternal line in the third intercostal space, from the mid-clavicular line in the fifth intercostal space, and from the anterior axillary line in the fourth intercostal space. Traces from the suprasternal notch, and the right epigastric and left epigastric regions are indicated by K_{ss}, K_{er}, and K_{el}, respectively.

The designation of the specific events of the cardiac cycle poses a more complex problem. One desideratum is that the motions be labeled in their normal sequence and according to some generally accepted subdivision of the cardiac cycle. Even though both dogs and men display a common general sequence, this is not absolute, and varies in detail from one individual to another within the same species. Likewise, there are relatively few subdivisions in Wigger's classic separation of the cardiac cycle, whereas the cardiac motions are much more numerous.

An ideal description of the cardiac movements would include both anatomic and physiologic components. One would like to know not only the precise structure responsible for, but also the exact mechanism whereby it produces, the motion in question. Although the studies seem to supply certain suggestive evidence related to these questions, there are several exceptions.

These considerations have led to the adoption of the following procedure in designating the movements. The major phases of the cycle of ventricular activity are indicated by the letters C (contractile movements observed between the onset of excitation and the start of left ventricular ejection), J (ejection), and R (relaxation). These letters are preferred to I (isometric) and E (ejection), in order to avoid confusion with the terms used in an earlier publication[1] from this laboratory, which was of a descriptive nature and was presented prior to recent information concerning the possible mechanism of the motions.

Between the times of excitation and of left ventricular ejection, 10 different precordial deflections are commonly seen. Therefore, for the purpose of simplicity, this period is subdivided into CI (start of excitation to beginning of first heart sound), CII (onset of first sound to beginning of right ventricular ejection), and CIII (right ventricular to left ventricular ejection). An attempt has been made to designate, by one or more letters and within parentheses, the specific structure* which is believed to be particularly related to the movement in question. Finally, in order to emphasize the distinction of the small motions from the larger ones, a capital letter is used in referring to the latter. The term *CI(pl)*, then, means that during isometric contraction, before the start of the first sound, a small motion is observed that is believed

*For footnote, see page 68.

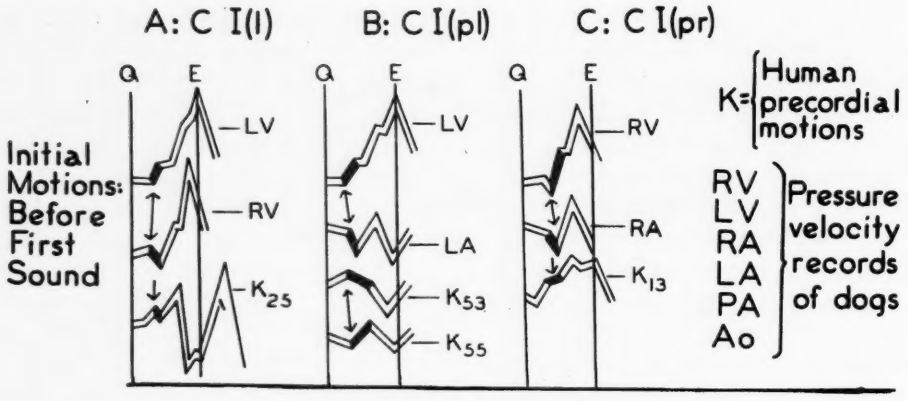

Fig. 2. *(For legend, see opposite page.)*

to be due to the contraction of the papillary muscles of the left ventricle. Likewise, the expression *CII(S)* indicates that contraction of the septum is thought to be responsible for a large motion occurring after the onset of the first sound but before the start of right ventricular ejection.

This system of nomenclature, although cumbersome, appears to be less confusing than the others which we have attempted.

Results

For the sake of clarity, the several motions of both species are integrated in Fig. 2. This is a diagram and displays those movements which were either invariably or frequently observed. The actual data from the human subjects are summarized in Table I and illustrated in Figs. 3, 5, and 7; those from the dogs are shown in Table II and Figs. 4, 6, and 8.

Terminal atrial movements at the onset of ventricular excitation. All subjects exhibited an outward motion starting just before or after Q in two or more of the right parasternal traces (Fig. 3, *C* and *D*). At the other precordial regions this upstroke was less frequently seen. These motions were small.

The atrial pressure velocity traces of the dogs commonly exhibited a slight decline, usually starting shortly before the beginning of ventricular excitation (Fig. 4).

COMMENT. In previous reports,[2] evidence indicating that these motions are of atrial rather than ventricular origin was presented. Thus, similar precordial movements are encountered after isolated P waves in patients with heart block and are absent in subjects with auricular fibrillation. Presumably, these deflections are related to relaxation of the left atrium. Filling of the atria as they relax is probably also concerned (Fig. 4).

Aside from the terminal atrial forces, a regular sequence of deflections due to ventricular activity was noted.

I. Initial ventricular motions starting before the first heart sound. At about 0.035 second after Q, three precordial motions were seen (Fig. 2, *A*, *B*, and *C*). All subjects exhibited outward or inward deflections in the K_2 and K_4 lines (Fig. 5). Most of them displayed inward motion in the right parasternal region (Fig. 3, *C* and *D*), and some showed reciprocal movement (inward above, outward below) in the left anterior axillary line (Fig. 3, *A* and *B;* Table I).

The conventional pressure records and the pressure velocity traces from the left ventricle of the dogs usually began to rise about 0.01 second before those from the right. In most of the animals the right ventricular velocity record showed a slight downward dip either before or just after its initial rise (Figs. 4 and 6).

*It should be realized that the designation of a given structure as being responsible for an observed motion is at present hypothetical and must be considered as tentative pending information secured by more direct means. For this reason the abbreviations which indicate structures are placed in parentheses. The division of the early portion of the cardiac cycle into three parts is an oversimplification. Actually, there is first a phase of electromechanical lag and then the three phases mentioned above. It should also be noted that the term *isometric contraction* as commonly used to indicate the period between the onset of the first heart sound and the start of ejection is different for the two ventricles because the right chamber ejects first in the normal human subject. Furthermore, the precordial traces exhibit ventricular motions which start 0.01 to 0.02 second before the first heart sound, and a similar phenomenon is seen in the pressure velocity traces of the dogs.

The atrial velocity traces commonly exhibited decline as the ventricular pressures rose (Fig. 4; Table II). This dip was sometimes preceded by an initial rise. These atrial motions were seen in an animal with heart block during ventricular complexes which were removed from P waves. They, therefore, are due to initial ventricular rather than to terminal atrial activity.

COMMENT. The findings illustrated in Fig. 4 indicate that at the onset of isometric contraction the interventricular septum of the dog tends to move to the left (pull

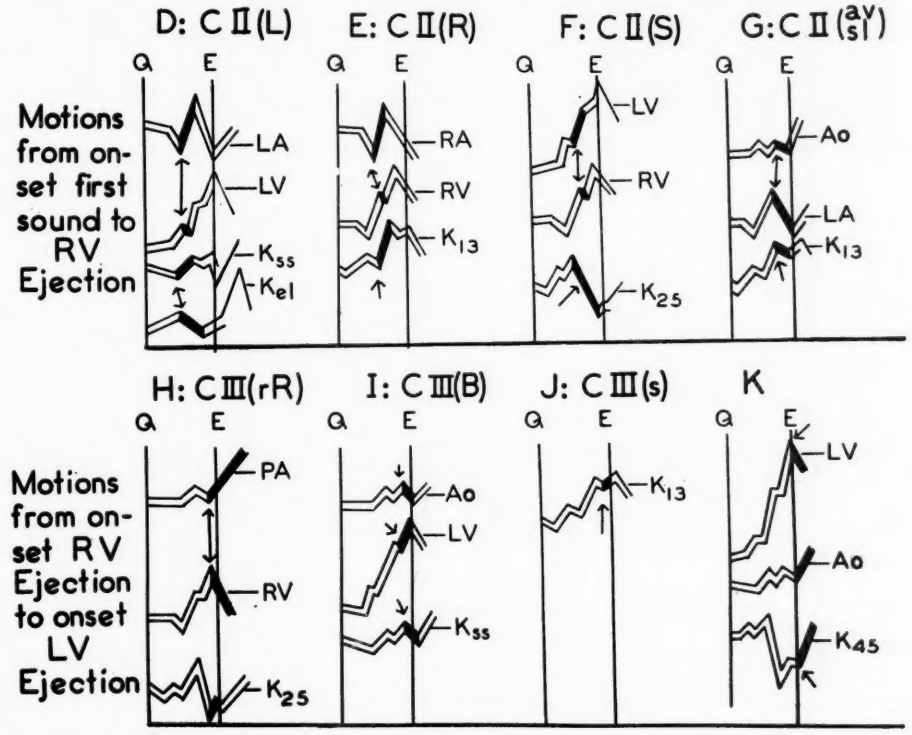

Fig. *2.* This diagram illustrates all of the motions occurring between the onset of excitation (*Q*) and the start of left ventricular ejection (*E*). The velocity traces (*vel*) of the dogs and the precordial movements (*K*) of the human subjects are adjusted to a time scale corresponding to an identical duration of isometric contraction in the two species. The specific motions are designated by the arrows and by the black areas. *A*, The downstroke in the precordial (K_{25}) and the right ventricular records as the left ventricular trace starts to rise are ascribed to a backward-leftward pull on the interventricular septum. *B*, The downstrokes in the left atrial and upper left axillary (K_{53}) records, associated with upstrokes in the left ventricular and lower axillary traces, are attributed to contraction of the left papillary muscles. *C*, Similar reciprocal changes in the right chambers and the small inward motion in the right parasternal (K_{13}) region probably represent right papillary contraction. *D*, The abrupt rise in the left atrial record is ascribed to mitral closure. At the same time the inward movement in the epigastrium (K_{el}) and the outward deflection in the suprasternal area (K_{ss}) point toward headward displacement of blood. *E*, Rightward motion of blood and tricuspid closure appear to be responsible for the upward deflections in the right parasternal area (K_{13}) and in the right atrial record. *F*, The large backward motion of the precordium (K_{25}) is accompanied by respective increase and decrease in the rate of rise in pressure in the left and right ventricles. These phenomena can be explained by contraction and leftward movement of the interventricular septum. *G*, Downstrokes in the atrial, aortic, and right parasternal records are ascribed to motion of the atrioventricular and, possibly, the semilunar rings toward the apex. *H*, The abrupt decrease in the velocity of rise in pressure in the right ventricle associated with the large upstroke in the pulmonary artery trace indicate right ventricular ejection, which is accompanied by a small forward (recoil) movement in the precordial (K_{25}) trace. *I*, The downstroke in the aortic and suprasternal (K_{ss}) records associated with steeper rise in pressure in the left ventricle point toward a downward pull on the aortic ring. *J*, The small outward motion in the right parasternal area is not regularly associated with analogous changes in the records from the dogs. It is uncertain whether this movement is related to rightward displacement of the interventricular septum or to bulge of the tricuspid valve into the right atrium. *K*, The end of the left ventricular isometric period is indicated by the abrupt upstroke in the aortic trace and the simultaneous decrease in the rate of rise in pressure in the left ventricle. At the same time the apical (K_{45}) trace shows a second and larger outward recoil. This motion [JI(rL)] is not labeled as such in the figure because it occurs during ejection rather than during isometric contraction.

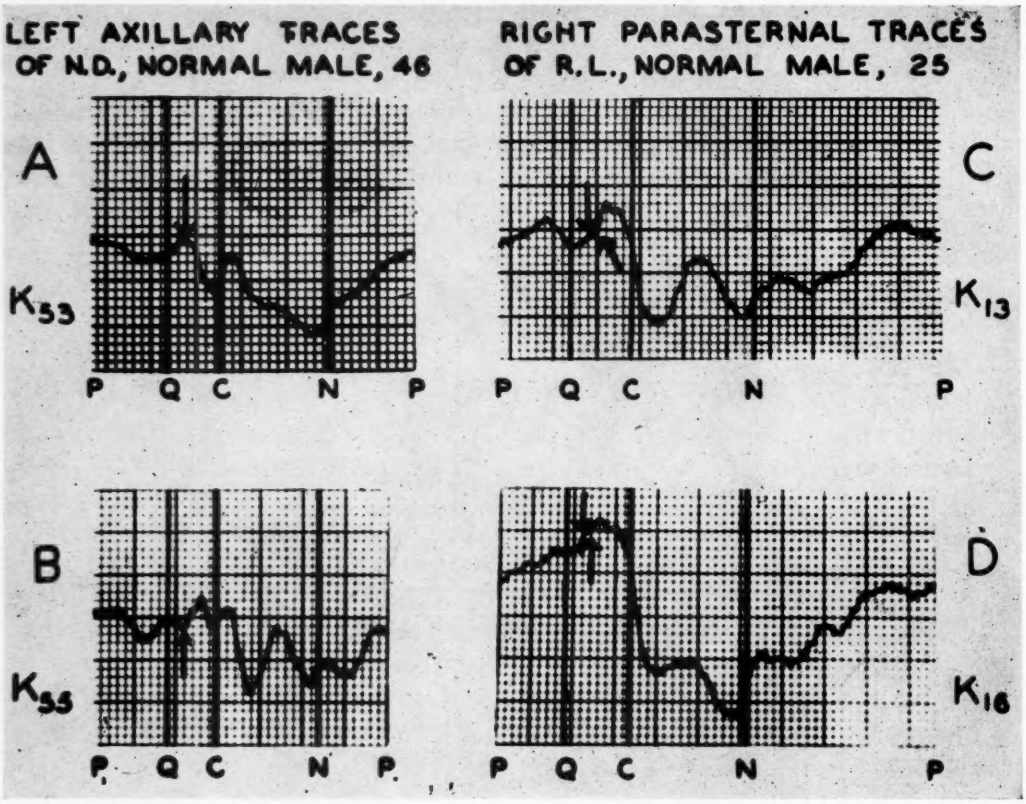

Fig. *3*. Some of the motions during isometric contraction. Paper speed, 50 mm. per second. All traces start and end at onset of the P wave. Vertical lines indicate onset of excitation (*Q*), of carotid upstroke (*C*), and of carotid incisural notch (*N*). *A* and *B*, At 0.04 sec. after Q a small inward motion is seen in the third intercostal space in the left anterior axillary line (K_{53}) at the same time at which outward movement begins in the fifth intercostal space (K_{55}). These deflections, which are more pronounced in this subject than in most others, are ascribed to contraction of the papillary muscles of the left ventricle. They are designated in the text as CI (pl). At 0.07 to 0.08 sec. after Q, both records exhibit downstrokes. These are possibly related to descent of the mitral annulus [$CII(^{av}_{sl})$] with decrease in the transverse diameter. *C* and *D*, Small upstrokes attributed to atrial relaxation occur as ventricular excitation starts. About 0.04 sec. later a minimal inward motion (*arrow from above*) is seen. This is believed to be related to contraction of the right papillary muscles and is called CI(pr) in the text. The next motion (*second arrow*) occurs about 0.02 sec. later, is outward, and is designated as CII(R). In this subject, as in most others, it is larger in the upper (*C*) than in the lower (*D*) right parasternal intercostal spaces. It appears to be closely associated with tricuspid closure (see text). Both traces exhibit very small inward, then outward, deflections after the second arrow and before the large downstroke which signifies the change in volume due to ejection. The small inward movement is designated $CII(^{av}_{sl})$, and is attributed to downward pull on the tricuspid annulus. The subsequent tiny upstroke is called CII(s) and is ascribed to rightward displacement of the interventricular septum.

by left ventricle). A similar explanation probably accounts for the inward motion sometimes seen in the left precordial (K_2 and K_4) records.* Since the left ventricle, which usually starts to contract first,[3,4] appears to be mainly responsible for this small initial motion, it is designated as CI(l).

*The initial outward motion which was often seen in these areas may be related to rightward displacement of the septum by the rising pressure in the left chamber.

The observation of reciprocal motion, with downstrokes in the upper and upstrokes in the lower intercostal spaces, in the left anterior axillary traces of some of the human subjects (Table I) accords well with the usual finding in the dogs (Table II). In the animals the left atrial velocity curves exhibited a decline soon after the left ventricular pressure began to rise. The similar phenomena observed in the right chambers of the dog appear to

correspond to the small inward motion of the human right parasternal region. These several findings point toward descent of the atrioventricular cusps. Conceivably, such motions might be due to a downward pull on the rings of these valves. However, it is more likely that contraction of the papillary muscles, which are excited early, is the mechanism responsible. These two movements are, therefore, tentatively designated as CI(pl) and CI(pr).

II. Movements occurring between the first heart sound and the onset of right ventricular ejection.

CII(L). HEADWARD MOTIONS AT THE TIME OF MITRAL CLOSURE. Three different observations in the human subjects suggested that blood was being displaced headward during the early phase of ventricular contraction, i.e., 0.04 to 0.07 second after the QRS onset. (a) Four individuals exhibited a downstroke in the epigastric traces (Figs. *2,D* and *7,A*), meaning either headward or backward motion of the inferior surface of the heart; at the same time, each of them had an outward motion in the second and third intercostal spaces at the K_2 or K_4 areas. (b) Five persons displayed an upstroke in the upper left precordial region, associated with the downstroke in the lower (fifth and sixth intercostal spaces) areas. (c) Six subjects exhibited a small upstroke in the trace recorded from the suprasternal notch (Figs. 2,*D* and 7,*B*). Nine of 10 persons exhibited one or more of these headward motions. The time of onset of

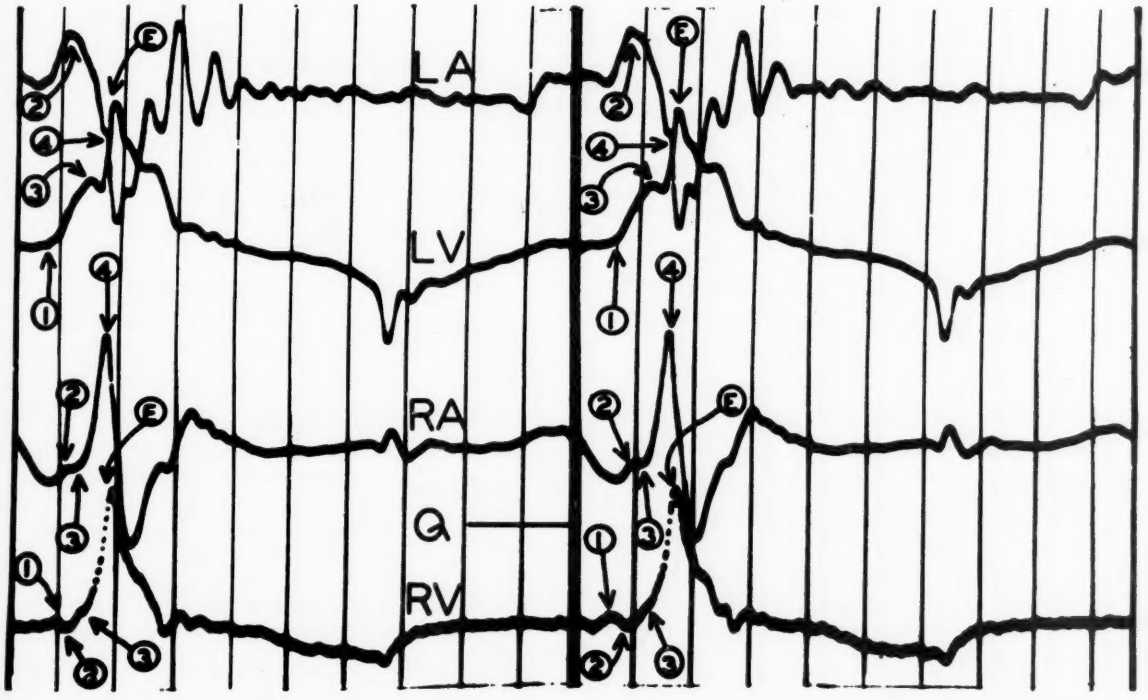

Fig. *4*. The pressure velocity curves of the four cardiac chambers of a dog are shown during two successive cycles, starting and ending at Q. Time lines are 0.04 sec. apart. As ventricular excitation starts, the atrial curves are declining (relaxation). The subsequent rise 0.02 sec. later is presumably due to atrial filling. *1*, At 0.03 sec. after Q the left ventricular trace (*LV*) begins to increase, whereas there is slight decline in the right ventricular record (*RV*). This is attributed to a leftward pull on the septum. *2*, About 0.04 sec. after the start of excitation the right ventricular pressure starts to rise and the atrial traces exhibit either a decline (*LA*) or an abrupt leveling of the previous upstroke (*RA*). These changes are ascribed to contraction of the papillary mucles, with downward motion of the atrioventricular cusps. *3*, As the right ventricular curve becomes steeper, there is a sharp upstroke in the right atrial trace, and at the same time the rate of rise in pressure in the left ventricle decreases. It would appear that the interventricular septum is being displaced to the right as ascent of the tricuspid leaflets occurs. The mitral closure upstroke in the left atrial trace was smaller (notch in the downstroke between second and fourth arrows) in this dog than in most. Ascent of the tricuspid leaflets occurred unusually early in this animal. *4*, The sharp decline in the rate of rise in ventricular pressure, denoting ejection (*E*), occurred 0.07 sec. after Q. About 0.01 sec. before this, both atrial traces displayed a sharp downstroke, which is attributed to descent of the atrioventricular rings toward the apex.

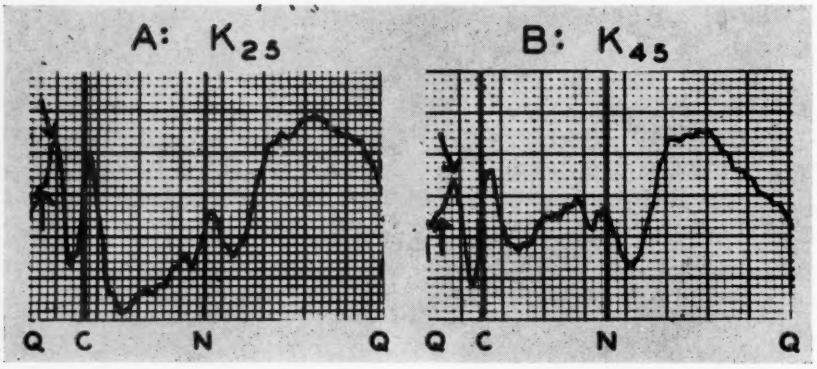

Fig. 5. Motions of the left lower precordial region during isometric contraction. Paper speed, 50 mm. per second. Traces start and end with ventricular excitation, illustrating one complete cycle. *C* and *N* refer, respectively, to start of carotid upstroke and to incisural notch. The outward motion as excitation starts is attributed to atrial relaxation. The second portion of this biphasic upstroke (*first arrow*) is probably related to change in shape of the right ventricle, and is due either to contraction of the papillary muscles or to displacement of the septum as the left ventricular pressure starts to rise [CI(1)]. The second arrows indicate the large inward motion of the fifth intercostal space in the left parasternal (*A*) and mid-clavicular (*B*) lines. This is ascribed to contraction and backward movement of the interventricular septum [CII(S)]. After the downstroke a large outward deflection is observed. The biphasic nature of this movement is clearly seen in *A*. The small initial component begins 0.09 sec. after Q and 0.04 sec. before the carotid upstroke. This movement is thought to represent right ventricular recoil, and is designated CIII(rR). The larger component which starts 0.02 sec. later and is also present in *B* is ascribed to left ventricular recoil.

these deflections corresponded with the beginning of the mitral first sound (0.053 ± 0.013 second) in 8 of 9 subjects.

At this time of the cycle, or about 0.01 second later, traces of pressure velocity from the pulmonary artery and from the aorta of dogs sometimes displayed a small rise (Fig. 6). All of the atrial traces showed either an upstroke or a notch in the downstroke previously mentioned (Table II; Figs. 4 and 8). The close relationship of this left atrial upstroke to the mitral first sound is indicated in Fig. 8.

Comment: These data point toward headward motion of the blood. In the case of the dogs the upstroke in the left atrial trace indicates mitral closure. The slight rise occasionally seen in the pressure velocity traces from the aorta and from the pulmonary artery signify bulge of the semilunar valves into the great vessels. The findings in the human subjects likewise point toward headward movement of blood as mitral closure occurs.

CII(R). RIGHTWARD MOTION AT THE TIME OF TRICUSPID CLOSURE. An upstroke was present in the right parasternal areas in each subject (Fig. 2,*E*). This outward deflection usually started 0.05 to 0.06 second after Q. The extreme limits were 0.03 and 0.075 second. The size varied from a flattening of the preceding downstroke (amplitude 0) to 5 mm. The absolute size was slightly greater, and the relative amplitude much larger, in the higher than in the lower intercostal spaces (Fig. 3, *C* and *D*), being somewhat larger in the second than in the others (Table III).

Comparisons were made in 9 normal subjects of the time of onset of this right parasternal outward movement and of the tricuspid component of the first heart sound. The latter phenomenon occurred within the range of 0.01 ± 0.01 second after the former.

Right atrial pressure velocity traces from the dogs showed a rise at about 0.05 second after the start of the QRS (Table II; Fig. 4). This motion corresponded in time to the tricuspid component of the first heart sound (Fig. 8).

Comment: These data suggest that the right parasternal outward motion which occurs about 0.055 second after Q is prob-

ably related to rightward displacement of blood as tricuspid closure occurs. The finding that this deflection is larger in the upper than in the lower intercostal spaces is in accord with this conclusion. In the human subjects the tricuspid component of the first sound occurred about 0.01 second after the cusps had begun to move toward the atrium.

The mechanism of this movement is probably different in patients with right ventricular hypertrophy, who usually display marked exaggeration of this deflection in the left as well as in the right parasternal region. In such persons the motion may be mainly due to forward rightward twist of the heart, as was described by William Harvey,[5] or to a forward bulge of the right ventricular wall as is indicated by the work of Anzola.[6]

CII(S). THE LARGE LEFT PARASTERNAL INWARD MOVEMENT. All of the records from the lower intercostal spaces in the left parasternal (K_2) and mid-clavicular (K_4) lines exhibited a downstroke. A similar but smaller movement was present in most of the traces from the upper intercostal spaces. This is usually the largest motion during isometric contraction (Fig. 5). It ordinarily begins 0.06 to 0.08 second after

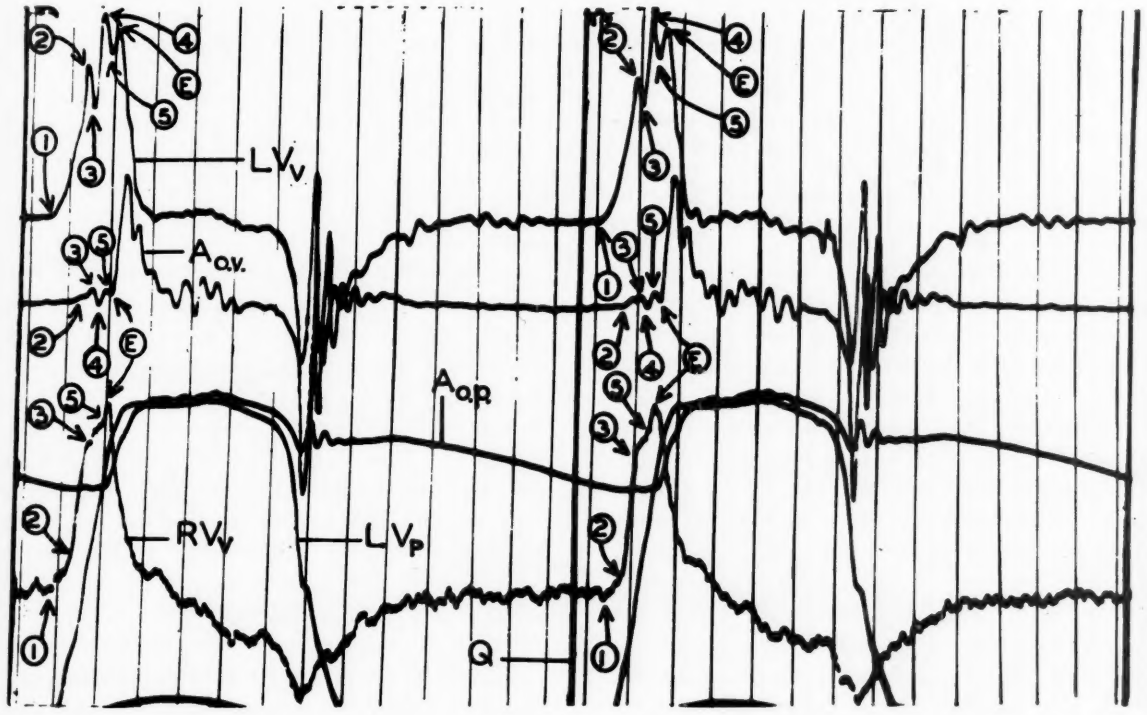

Fig. *6*. Pressure velocity changes during isometric contraction, in a dog. Two complete cycles, starting and ending at Q, are shown. Time lines indicate 0.04 sec. The pressure velocity traces (*v*) of the left and right ventricules and of the aorta, as well as the undifferentiated pressure records (*p*) of the aorta and of the left ventricle are shown. The greater detail of the velocity traces is illustrated. *1*, At 0.03 sec. after Q: Both ventricular velocity traces begin to rise but there is soon a slight flattening of the right record. This is ascribed to an early leftward pull on the septum. *2*, At 0.06 sec. after Q: As the velocity of rise in pressure in the right ventricle suddenly increases, there is a corresponding decline on the left, whereas the slight rise in the aortic trace suggests headward displacement of blood, with bulge of the aortic cusps. It is uncertain whether the latter factor or displacement of the interventricular septum to the right is the cause of the dip in the LV trace. *3*, At 0.065 sec. after Q: The interventricular septum appears to enter into contraction, causing respective rise and fall in the rate of rise in pressure in the left and right ventricles. At the same time there is a downstroke in the aortic trace, indicating the first of two footward pulls on the aortic ring. This was associated with a sharp downstroke in the atrial velocity traces (Fig. 4, *arrow 4*). *4*, At 0.075 sec. after Q: A second bulge of the aortic cusps probably explains the decline in the left ventricular, and the increase in the aortic, velocity traces. *5*, At 0.085 sec. after Q: The second downstroke in the aortic velocity record, associated with sharp rise in the left ventricular trace, points toward a second descent of the aortic ring. *E*, At 0.09 sec. after Q: Ejection of both ventricles is indicated by the sudden decrease in their pressure velocity traces and the abrupt upstroke in the aortic record.

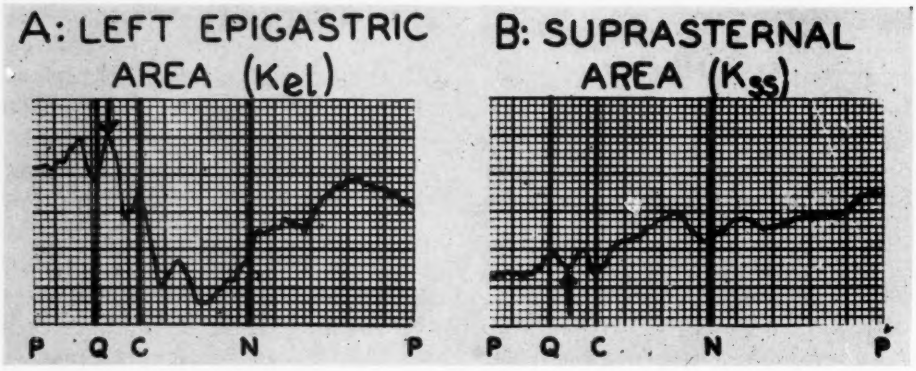

Fig. 7. Headward displacement of blood at the time of mitral closure, in T.H., a 59-year-old normal male subject. Paper speed, 50 mm. per second. Traces depict one cardiac cycle starting and ending with the P wave. The onsets of excitation (*Q*), of the carotid upstroke (*C*), and of the carotid incisural notch (*N*) are shown by the vertical lines. Headward displacement of blood at 0.04 to 0.05 sec. after Q is illustrated by the arrows. Thus, the epigastric and suprasternal records show inward and outward motion, respectively, at this time. This motion is designated in the text as CII(L). At 0.08 sec. after Q, and again at 0.10 sec., *A* displays small upstrokes attributed to footward recoil as the two ventricles eject successively. The suprasternal trace exhibits a prominence of the downstroke occurring 0.09 sec. after Q and 0.03 before the carotid upstroke. This motion is designated as CIII(B) and is attributed to footward pull on the aortic ring by the muscles at the base of the left ventricle.

excitation starts and is greater in the lower than in the upper intercostal spaces (Table III). Corresponding deflections were not regularly encountered in the traces from right parasternal, epigastric, or axillary regions. The suprasternal records sometimes exhibited an upstroke or a continuation of the previous one.

A corresponding motion was occasionally encountered (Fig. 8) but not regularly seen in the dog at this phase of isometric contraction. A reciprocal ventricular relationship, rise of pressure velocity on the left and fall on the right, occurred earlier and has already been described [CI(l)].

Comment: The observations in human subjects suggest that the movement in question is related to contraction of the interventricular septum. Keith[7] and, later, Grant[8] have indicated that this structure is functionally a part of the left ventricle. During diastole it is rounded with rightward convexity. Therefore, the shortening associated with contraction pulls the septum leftward and backward. If the corresponding motion occurs in the dog, it either appears sooner or is masked by the rightward displacement at the time of tricuspid closure (Table II).

The outward motion in the suprasternal notch which sometimes occurred at this time is attributed to a second bulge of the aortic cusps. This was reflected in the dogs by an upstroke in the velocity traces from the aorta and from the pulmonary artery (Fig. 6; Table II).

If the precordial downstroke under discussion is actually the result of contraction of the interventricular septum, the data in Table III suggest that the lower portion contracts before the upper. This is in accord with the known sequence of septal excitation.[9-11]

CII $\binom{av}{sl}$. SMALL INWARD RIGHT PARASTERNAL MOTIONS. All of the subjects exhibited minimal downstrokes in the K_1 areas at 0.075 to 0.08 second after Q (Figs. 2,*G* and 3,*C* and *D*). Similar motions were occasionally observed in the K_5, epigastric, and suprasternal traces. The K_2 and K_4 records often showed decreasing steepness of the previous large inward deflection.

The dogs regularly displayed an abrupt downstroke in the left atrial record (Fig. 4, *arrow 4*) and a smaller downstroke in the aortic traces (Fig. 6, *arrow 5*). Similar findings were sometimes, but less consistently, seen in the right atrial (Fig. 4, *arrow 4*) and pulmonary arterial records.

Comment: These several findings can all be explained by the assumption that

muscles which are attached to the rings of the atrioventricular and semilunar valves begin to contract at this time. The motion is, therefore, designated as CII($^{av}_{sl}$). The presence of a downstroke (signifying headward motion of the inferior border) in some of the epigastric records would suggest that these muscles are those which pass

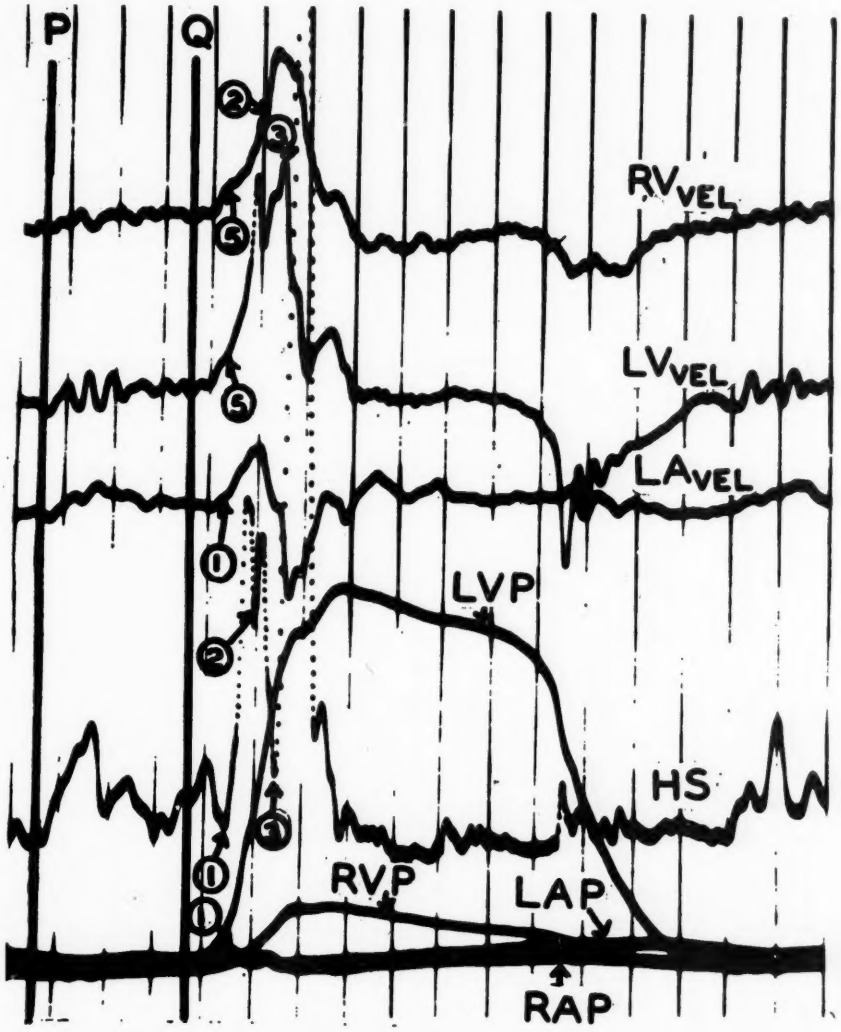

Fig. *8*. First heart sound in relation to pressure velocities. The pressure pulses from the left (*LVP*) and right (*RVP*) ventricles and the left atrium (*LAP*) and right atrium (*RAP*), and the pressure velocity (dP/dt) traces (*vel*) from the two ventricles and from the left atrium of a dog are shown. The heart sounds (*HS*) were recorded from the free wall of the left ventricle by a technique which depicts the "intensity envelope" of the sound vibrations (sonvelogram). Three components of the first sound are seen: *1*, The first major component coincides with a sharp upstroke of the left atrial velocity trace and the C wave of the atrial pressure. *2*, The second component of the first sound is associated with a phase of rapid rise in pressure in the right ventricular record. At the same time the right atrial velocity trace (which is not shown here) exhibited an abrupt rise. These phenomena, ascribed to tricuspid closure, occur very early in the course of the rise in right ventricular pressure. *3*, The unusually large third component is probably an ejection sound, since it occurs simultaneously with the abrupt downstroke of the left ventricular velocity trace that has been associated with left ventricular ejection in all dogs in which simultaneous central aortic pressures were recorded. The decrease in slope of the right ventricular velocity trace, labeled *S*, associated with increased steepness of the left ventricular velocity trace, is probably due to leftward displacement of the interventricular septum (see text).

Table I. *Precordial motions during the period between the onset of excitation and the start of left ventricular ejection*

Movement		*Description*	*Of 10 subjects, present in:*	*Average time after Q (sec.)*	*Probable mechanism*	*Remarks*
Terminal atrial		↗ K_1	10	0.005	Atrial relaxation	Frequent in other precordial areas. Often precedes Q
Initial ventricular before onset of first sound	CI(l)	↘ or ↗ K_2 to K_4	10	0.037 ± 0.012	Displacement of IV septum by LV	Either pull (↘) or push (↗) may predominate
	CI(pl)	↘ Upper K_5 ↗ Lower K_5	5 (both)		Contraction of left (pl) and right (pr) papillary muscles	Very small; often confused by preceding and succeeding motions
	CI(pr)	↘ K_1	8			
First sound to right ventricular ejection	CII(L)	↗ High areas ↘ Low areas	9 (at one or more areas)	0.053	Mitral closure: headward displacement of blood	Coincides with mitral Sl. Bulge of aortic cusps and of outflow tract
	CII(R)	↗ K_1	10	0.055	Tricuspid closure: rightward displacement of blood	About 0.01 sec. before tricuspid Sl. Also at K_2 areas in patients with RVH
	CII(S)	↘ K_2 to K_4	10	0.068	Contraction of IV septum	Larger and earlier at lower than at upper areas
	CII( )	↘ K_1 ↘ K_{ss}; KE	K_1: 10	0.078	Descent of valve rings	Often masked in suprasternal and epigastric areas
RV ejection to LV ejection	CIII(rR)	↗ Lower K_2	9	0.088	RV recoil	Often fused with later and larger LV recoil
	CIII(B)	↘ K_{ss}	10	0.091	Descent of aortic annulus	Sometimes visible in carotid pulse
	CIII(s)	↗ K_1 ↘ K_5	K_1: 10 K_5: 6	0.095	Displacement of IV septum to right (?)	Also possibly bulge of tricuspid leaflets

LV: Left ventricle. RVH: Right ventricular hypertrophy. IV: Interventricular.

Table II. *Pressure velocity changes in dogs during isometric contraction*

	Before onset of first heart sound				*First heart sound to ejection*				
Motion	*Gradual atrial* ↘	*Onset ventricular* ↗	*Abrupt atrial* ↘	*RV* ↘ *or less* ↗ ; *LV* ↗	*LA* ↗ ; *LV* ↗	*RA* ↗ ; *RV* ↗ ; *LV* ↘ *or less* ↗	*Ao* ↗ ; *PA* ↗ ; *RV* ↗ ; *LV* ↘ *or less* ↗	*Ao* ↘ ; *LA* ↘ ; *LV steeper* ↗	*Ao* ↗ ; *PA* ↗ ; *LV* ↘ ; *RV* ↘
Number of dogs studied*	RA 7 LA 8	LV 18 RV 15	LA 14 RA 14	15	13	12	Ao 6 PA 7	7	7
Number showing motion	RA 7 LA 8	LV 18 RV 15	LA 12 RA 10	14	13	12	Ao 6 PA 7	7	3 PA first 4 PA and Ao simultaneous
Average time after Q (sec.)	0.01 Before Q	LV 0.02 RV 0.03	LA 0.02 RA 0.03	0.04	0.04	0.05	0.05	0.06	0.08
Probable mechanism	Atrial relaxation	LV usually begins to contract first	Contraction of papillary muscles	LV tug on IV septum	Mitral closure	Tricuspid closure. Displacement of IV septum to right	Bulge of semilunar cusps	Descent of aortic and mitral rings	Ejection: either RV first or simultaneous
Remarks	May start after Q			Coincides with next motion	Coincides with mitral first sound	Coincides with tricuspid first sound	Coincides with previous motion	PA only occasionally shows similar ↘	

*Only those records which were technically good were analyzed for this table. Hence the number of observations differed for different phenomena.
LV and RV: Left and right ventricles. LA and RA: Left and right atria. Ao: Aorta. PA: Pulmonary artery. IV: Interventricular.

Table III. *Times and amplitudes of certain precordial motions during isometric contraction*

Intercostal space	*Right parasternal outward movement**				
	2nd (K_{12})	*3rd* (K_{13})	*4th* (K_{14})	*5th* (K_{15})	*6th* (K_{16})
Of 10 persons, present in	10	10	9	7	7
Average time after Q (sec.)	0.055	0.055	0.058	0.052	0.058
Average amplitude (mm.)	2.3	1.6	1.5	1.3	1.6
Average total amplitude of trace (mm.)	12.6	16.6	19.8	22.1	24.0

*This is designated as CII(R) and is apparently related to tricuspid closure.
†This is designated as CII(S) and is ascribed to contraction of the interventricular septum.

down from these rings and make up the lower margin of the ventricles. There also appears to be a tendency toward shortening of the transverse diameter and increase in the anteroposterior dimension of the heart at this time.

The decline in the atrial velocity traces was of brief duration but was of large amplitude. However, the actual change in pressure was often small, and in some instances could have been overlooked in the orthodox pressure records. Because the derivative traces reflect the velocity rather than the degree of change, they supply more information concerning the qualitative aspects of contraction.

III. Motions starting between right and left ventricular ejection.

CIII(rR). SMALL OUTWARD MOTION IN THE LOWER LEFT PARASTERNAL AREA. Such a movement was seen at about 0.085 second after Q in 9 of the 10 human subjects (Figs. 2,*H* and 5,*A*). The only direct analogue observed in the dogs was the rise in pressure in the pulmonary artery.

Comment: Evidence has been advanced in a previous publication[12] that this precordial motion is due to forward-footward recoil as the right ventricle ejects. It is usually succeeded in about 0.02 second by a steeper and larger movement (Fig. 5,*A*), which is attributed to left ventricular recoil. Under the conditions of the animal experiments this asynchronism of ejection was less consistent. The large upstroke indicating ejection often occurred simultaneously in the pulmonary artery and in the aorta of dogs (Table II).

CIII(B). DOWNWARD MOVEMENT IN THE SUPRASTERNAL NOTCH. This was observed in each of the 10 subjects at about 0.09 second after Q (Fig. 7,*B*) and was seen occasionally in the carotid pulse. It is attributed to a downward pull on the aortic annulus by the muscles at the base of the left ventricle.

Some of the dogs exhibited a continuation of the similar movement which had started somewhat earlier [CII($^{av}_{si}$)], but others displayed two different downstrokes of the aortic velocity trace, the last occurring just before the large upstroke of ejection (Fig. 6, *arrow 5*).

CIII(s). OUTWARD MOTION IN THE RIGHT PARASTERNAL REGION. These were seen in all subjects at about 0.095 second after Q (Figs 2,*J* and 3,*C* and *D*). If such movements occurred in the left parasternal area, they were obscured by the immediately preceding and succeeding right and left ventricular recoil deflections. Six of the 10 subjects displayed simultaneous inward motion in one or more of the lower left anterior axillary records.

Motions corresponding to this one were not observed in the dogs, possibly because

Left precordial inward movement†

Parasternal					*Mid-clavicular*				
2nd (K_{22})	*3rd* (K_{23})	*4th* (K_{24})	*5th* (K_{25})	*6th* (K_{26})	*2nd* (K_{42})	*3rd* (K_{43})	*4th* (K_{44})	*5th* (K_{45})	*6th* (K_{46})
9	10	10	10	10	8	8	8	10	10
0.071	0.069	0.067	0.065	0.064	0.073	0.071	0.066	0.065	0.066
2.8	5.4	9.6	11.2	9.7	3.0	4.5	6.4	6.7	6.0
14.7	20.0	29.8	28.7	27.3	10.8	19.3	21.5	21.8	19.7

the two ventricles tended to eject together.

Comment: It is possible that this small K_1 outward motion may represent a bulge of the tricuspid leaflets due to the rising pressure in the right ventricle. However, the frequent presence of a simultaneous inward deflection in the lower K_5 records suggests that the interventricular septum may now be displaced to the right as the right ventricle rapidly ejects. Therefore, the movement is tentatively designated as CIII(s).

The next motion, that of left ventricular recoil (Fig. 2,*K*), signals the end of isometric contraction and will be discussed in a subsequent report.

Discussion

The sequence of events observed in the precordial movements of man and in the pressure velocity traces of dogs exhibited certain differences. One of these concerned the relative duration of isometric contraction in the two ventricles. This was always longer for the left ventricle in the human subjects, a finding which agrees with the data obtained by cardiac catheterization.[3,4] In the dogs this difference was inconstant, and simultaneous ejection often occurred.

The other difference was in regard to the deflections which are considered to indicate movements of the interventricular septum. In the dog this structure appeared to be initially pulled leftward, whereas the human data indicated either a leftward-backward pull or a rightward-forward push as the left ventricle began to contract. The two later motions ascribed to the septum (contraction with leftward movement and rightward displacement) occurred in a constant relationship to the entire sequence in the human subjects but were variable in time in the dogs. To what extent these inconsistencies are a reflection of the artificial conditions—anesthesia, open chest, cannulation of cardiac chambers—in the animals or represent a difference between the species is not clear from this study.

Comparison of Tables I and II indicates that the similarities in the contraction sequence are much more numerous than the differences. Interpretations, such as these, which are based on indirect methods are subject to reservation. However, the observation that, with the exceptions mentioned, each regularly occurring precordial deflection apparently had an analogue in the animals, despite the use of an entirely different technique, supports the validity of the interpretations.

The data suggest that in both species the sequence of contraction may be approximately as follows. The process begins in the left ventricle and in the left and right papillary muscles about 0.03 to 0.04 second after the start of excitation. The

inferior portions of the two ventricles then shorten, pushing the atrioventricular cusps headward and causing the first sound, the mitral component occurring slightly before the tricuspid. In the human subject the interventricular septum now contracts and moves toward the left ventricle. Then those fibers (probably subepicardial) which are attached to the valve rings, and which encircle the inferior margin, begin to shorten. The consequent tendency toward decrease in both the transverse and the vertical dimensions causes headward bulge of the semilunar and, less consistently, of the atrioventricular cusps. Bulging of the free ventricular walls probably also occurs[6,13] but is not shown in the dogs by the techniques employed in this study, and is usually masked in the human precordial traces by the large preceding (septal contraction) and succeeding (recoil) deflections. A second downward pull on the aortic annulus by the left ventricular basilar muscles occurs either just before (dog) or after (man) right ventricular ejection. As this chamber begins to empty, the septum is displaced to the right.

It may be noted that the spread of the contractile process from subendocardial to subepicardial fibers and from apex to base is similar to the general sequence of the spread of excitation reported by numerous investigators. In the normal human being the contraction starts about 0.035 second after the beginning of excitation, and almost all fibers appear to have entered into contraction by 0.105 second. This duration of 0.07 second corresponds reasonably well with the average duration of the QRS complex. It would seem to follow that the electromechanical lag is essentially constant in the different portions of the ventricular muscle.

Some years ago, Isaac Starr and associates[14] demonstrated that the destruction of the entire free wall of the right ventricle was well tolerated by dogs. The evidence in the present study that the interventricular septum is displaced to the right by the higher pressure in the left ventricle may offer an explanation for this surprising phenomenon.

The fundamental studies of Otto Frank, Starling, Wiggers, and of their pupils established the important relationship between the strength of contraction and the existing state of the ventricular muscle immediately prior to it. The natural consequence has been a tendency to use the end-diastolic pressure as a guide to the initial length and/or tension. Our results suggest that this is an oversimplification. While the contractile process is still spreading, the pressure is rising, and changes in shape are occurring. As some fibers enter into contraction, others are being passively stretched. Both processes, the increase in radius and the rise in pressure, will augment the tension in the still uncontracted areas. It is not necessary to enter into the long-debated question of the relative importance of initial length as compared to initial tension to point out that both factors are increased in the late-contracting fibers by the effects of the fibers which start the process. In any case, the end-diastolic pressure is a guide to the initial state of only those fibers which contract early.

The observations suggest that the concept of isometric contraction, although useful and valid in relation to an entire ventricle, is not strictly applicable to the individual fiber. During sequential contraction, actual shortening of some fibers occurs prior to ejection, and is reflected by changes in the shape of the ventricular cavities, even though the volume remains constant. These conclusions are in accord with those previously advanced by Rushmer.[13]

After myocardial infarction[15] and during anginal attacks,[16] many patients exhibit marked bulges of the ischemic areas. Aside from the weakened contraction of the directly involved muscle, such bulges would appear to have an additional untoward effect. When, as is sometimes the case, they appear during the isometric phase, the shift of blood into the bulging area will reduce the radius and hence the tension of the healthy fibers.

The papillary, apical, and right ventricular muscle bundles which contract early are thin as compared to those of the septum and of the free wall of the left ventricle, which shorten later. The deep bulbospiral muscle which encircles the left ventricular outflow tract, and which appears to be the last of the major structures to contract, is the thickest of the bundles.

Other factors being equal, a given pressure will cause greater initial length and tension in the groups of thinner fibers. The sequence of contraction herein described is, therefore, mechanically advantageous. At the relatively low end-diastolic pressure, only those bundles which are thin, and thus more stretched, begin to shorten. As the pressure increases, the thicker but as yet uncontracted bundles are stretched. Thus, their initial state becomes more favorable as regards tension and length when they finally enter into contraction. The quantitative significance of this effect needs further investigation. In any case, the hemodynamic consequences of disordered intraventricular conduction would appear to merit analysis in relation to this general concept.

It should be emphasized again that these general concepts of cardiac motion are based on tentative hypotheses derived from indirect methods. Attempts to confirm or disprove these concepts by more direct techniques are in progress.

Summary

The sequence of human precordial movements prior to ejection has been compared with the rate of alteration in pressure in the cardiac chambers and great vessels of dogs. By the latter technique, simultaneous reciprocal changes in adjacent chambers appear to provide suggestive information concerning the movements of the intervening structure. Thus, a sharp decline in the aortic curve associated with increased rate of rise in the left ventricle may signify a downward pull on the annulus of the closed aortic valve. Similar indirect evidence concerning the movements of the interventricular septum, the atrioventricular cusps, etc., was obtained and utilized as a means of arriving at a tentative interpretation of the precordial movements.

Pending evidence obtained by more direct techniques, we believe that the sequence of motions prior to ejection is as follows.

The small initial deflections appear to begin in the left ventricle and in both sets of papillary muscles. Then there seems to be headward and, soon, rightward motion of blood associated with mitral and tricuspid closure, respectively. This is followed by a large backward precordial movement, which is assumed to be due to contraction of the interventricular septum. The next motion is a pull of the several valve rings toward the apex, producing a tendency toward shortening of both the transverse and vertical dimensions of the ventricles. At the same time, there appears to be headward bulge of the still closed semilunar valves.

As the right ventricle starts to eject, three additional motions occur. These are ascribed to (1) a small forward-footward recoil, (2) a second downward pull on the aortic ring, and (3) displacement of the interventricular septum to the right. When the isometric period of the left ventricle ends and its ejection begins, a larger recoil motion is seen.

According to these interpretations, the spread of contraction is similar to that of excitation. Throughout the ventricular mass the electromechanical lag appears to be relatively constant and about 0.035 second in man.

End-diastolic pressure is probably an accurate guide to the initial state of only those fibers which begin the contractile process. The rise in pressure so induced stretches further the uncontracted parts and thus changes favorably the initial tension and length of the fibers which contract later.

The mechanical advantage of this process, which involves original contraction of the thinner muscle bundles and utilization of the pressure so generated to increase further the stretch and, hence, the force of shortening of the late-contracting thicker bundles, is indicated.

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Model studies on the effect of the intracardiac blood on the electrocardiogram

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Although a number of experiments have been carried out on the effect of tissue inhomogeneities on the electrocardiogram, relatively little has been done on the possible influence of intracardiac blood. Measurements of tissue conductivity have demonstrated a considerably lower resistivity for blood than for other tissues. Reported ratios of blood resistivity to muscle resistivity have varied from nearly one half to one tenth.[1-4]

In order to study this effect, we have carried out experiments using artificial dipoles within or adjacent to excised hearts or appropriate heart models suspended in a volume conductor. The influence of intracavitary fluids of different resistivities was estimated from leads recorded from the periphery of the tank in which "heart" and dipole had been submerged.

Methods

Dog hearts were used in the initial experiments.[5] In some cases the hearts were left in situ, and tubing was connected so that the test fluid would run through the cavities and back out to a collecting bottle. The dipole, consisting of two probe electrodes, was placed within the cavity or into the myocardium tangential to the endocardial wall. The thorax incision was stitched together and the dipole potentials recorded in limb and chest leads. In some experiments the hearts were excised and immersed in an elliptical cylinder model of the human thorax. Potentials were then measured from electrodes at various points on the wall of the tank. NaCl solutions were used in the tank and for the cavity test fluids. The tank-fluid resistivity was 1,000 ohm-cm., and the perfusate values varied from 120 to 1,100 ohm-cm.

In later experiments[6] a small metal sphere was placed in the tank to represent the blood-filled cavity. The tank-fluid resistivity was again about 1,000 ohm-cm. With this model it was possible to study the effect of the angle of the dipole with respect to the wall of the sphere, and the distance between the dipole and the sphere,

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This project was supported by Grants H-2590 and H-2072 from the U. S. Public Health Service, and by a grant from the Maine Heart Association.
Received for publication Dec. 23, 1960.
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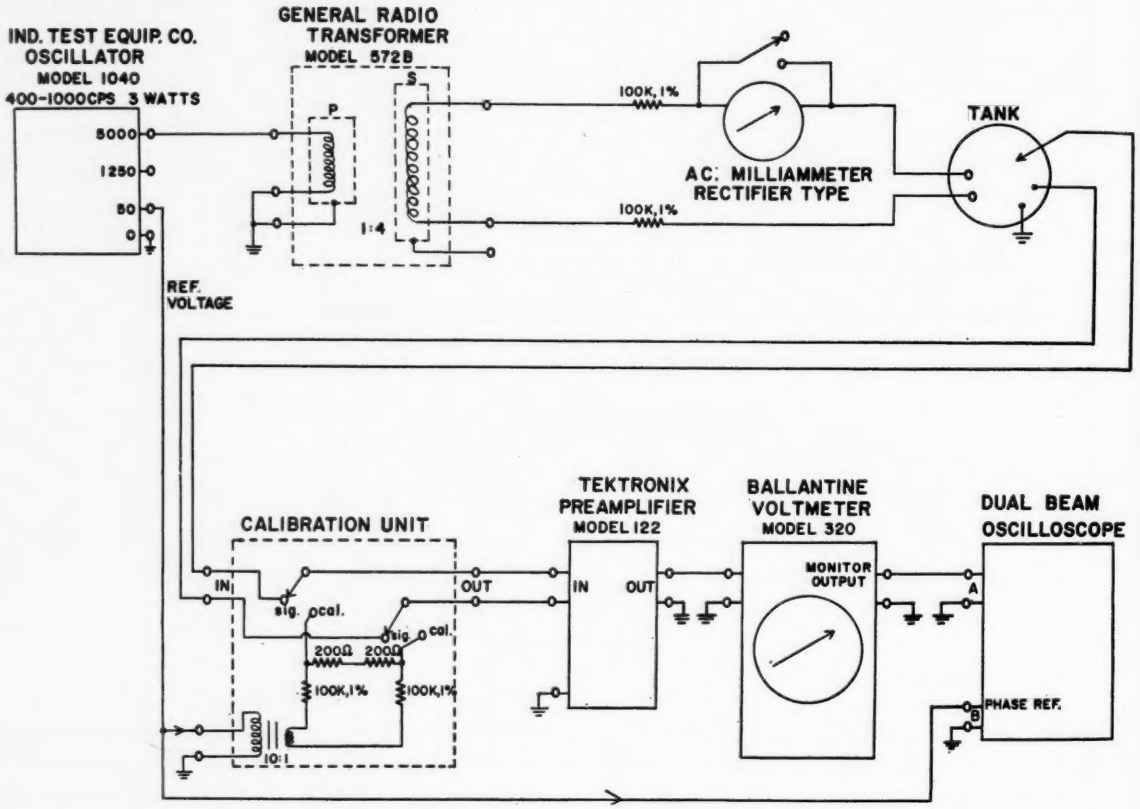

Fig. *1*. Dipole-energizing and potential-measuring circuits. The dipole-energizing voltage at a frequency of 400 or 1,000 cycles is obtained from the power oscillator. The oscillator voltage is stepped up to about 300 volts by the shielded transformer. High series-resistors cut down the voltage across the dipole to a few volts. Constant-current feed is used, and this, in conjunction with the series-resistance, eliminates the effects of electrode polarization. The tank voltages are applied through a differential amplifier to a direct-reading vacuum-tube voltmeter. The signal voltage is defined as being positive or negative, depending on whether it is in or out of phase with a reference voltage.

on the recorded peripheral potentials. In all cases the dipole was kept fixed, and measurements were made with the sphere out of the tank and then at different small distances from the dipole.

Finally, these measurements were repeated using dog bladders perfused with NaCl solutions to represent the cavity.[7] A double-lumen cannula was inserted into the urethra and tied in place. The two ureters were ligated. The test fluids were introduced through one tube and allowed to flow out through the other. After the bladder was filled with fluid, the double-lumen cannula was clamped. Again in studying the effect of distance, the dipole was kept fixed and the bladder moved.

The dipole-energizing and potential-measuring circuits are shown in Fig. 1. Constant-current dipole feed was used at a frequency of 400 or 1,000 c.p.s. To determine phase or polarity the signal and reference voltages were applied to the oscilloscope to give a Lissajous pattern, since this was found to be the most sensitive indication.

Results

This paper describes mainly the results obtained using the dog bladder to represent the blood-filled cavity. In the early experiments using dog hearts, with a resistivity of intracardiac fluid about one fifth that of the tank fluid, a reduction in potentials of about 25 per cent was observed with a tangential or intracavitary dipole, as compared with a homogeneous medium. The results using the metal sphere differed only in degree from the results using the bladder. The sphere corresponded to the limiting case of essentially zero resistivity for the internal fluid.

The dog hearts could be perfused by

fluids of different resistivities, but had certain disadvantages. It was difficult to obtain a leak-proof preparation, and in some cases the resistivity of the myocardial tissue itself apparently changed during an experiment. Also, it was very difficult to study the effect of the distance of the dipole from the endocardial wall or the effect of the relative dipole angle. For these reasons, attempts were made to find an alternative medium having a finite value of resistivity which could be immersed in the tank. Conductive silicone rubber proved unsatisfactory because of the difference in dielectric constant between the rubber and salt solution. According to Smythe,[8] if the dielectric constants of two conducting media differ and are not proportional to the conductivity, an additional boundary condition must be satisfied. In this case, a charge distribution is set up on the boundary.

The dog bladder proved to be an ideal solution to the problem, since the problem of dielectric constants was eliminated, and the cannulation of the bladder was very simple.

The positions and orientations of the dipole in the tank for each of the experiments are summarized in Table I. The x and y coordinates are defined in relation to the center of the tank. The positive values of x are toward the left side, and the positive values of y are toward the front. The semimajor axis (X) is 16.0 cm. and the semiminor axis (Y) is 12.8 cm. Platinum electrodes, ½ inch in diameter, were mounted around the wall on a horizontal level about three tenths of the depth of the tank from the top. The depth of the fluid was 43.5 cm. Other electrodes were used to simulate the limb leads. The z coordinate in the table refers to the position of the dipole center above (+) or below (−) the circumferential electrodes. The spatial dipole angle α refers to the angle of the dipole with the horizontal plane, whereas β is the angle between the projection of the dipole on the horizontal plane and the + X axis.

In the first series of experiments (with 1959 dates in Table I) the dipole used consisted of two spherical electrodes, 0.43 cm. in diameter, with an effective inter-

Table I. *Physical arrangements in 13 experiments using the dog bladder*

Experiment	*Location of dipole in tank (cm.)*			*Spatial angle of dipole*		*Angle between dipole axis and bladder wall*	*Ratio of bladder to tank - fluid resistivity = G*	*Distance of dipole center from bladder wall (mm.)*	*Bladder volume (ml.)*
	x	*y*	*z*	α	β				
First series:									
Jan. 23, 1959	8	5	1	0°	100°	0° (tang.)	0.16, 1.00	10	270
Feb. 5, 1959	7	6.5	0	0°	±180°	90° (rad.)	0.16, 0.96	10	200
Feb. 28, 1959	1.5	6.5	1	0°	±180°	90°	0.22, 0.29, 1.05	10	—
March 6, 1959	4	2	−0.5	0°	10°	90°	0.14, 0.33, 0.61, 0.88, 1.15	10	182
April 3, 1959	7.5	4.5	0	0°	110°	0°	0.14, 0.34, 0.64, 0.89, 1.18	1	640
April 16, 1959	5.5	2.5	2	0°	135°	45°	0.34, 0.42, 0.62, 0.95, 1.23	4.5	142
April 30, 1959	2	5	1	0°	90°	45°	0.135, 0.33, 0.61, 1.00, 1.24	4.5	250
May 8, 1959	5	3	1	0°	110°	30°	0.13, 0.31, 0.57, 0.90, 1.18	3	390
Second series*:									
Jan. 8, 1960	10	3	2	0°	100°	0°	0.15	2, 7, 12	—
Jan. 9, 1960A	5	5	0	0°	0°	90°	0.155	2 to 42	—
Jan. 9, 1960B	5	5	0	0°	−90°	0°	0.15	2 to 31	—
Feb. 3, 1960	6	3	0	0°	55°	45°	0.15	2 to 32	—
Feb. 4, 1960	3	7	−3	30°	60°	45-60°	0.145	2 to 32	—

*New dipole.

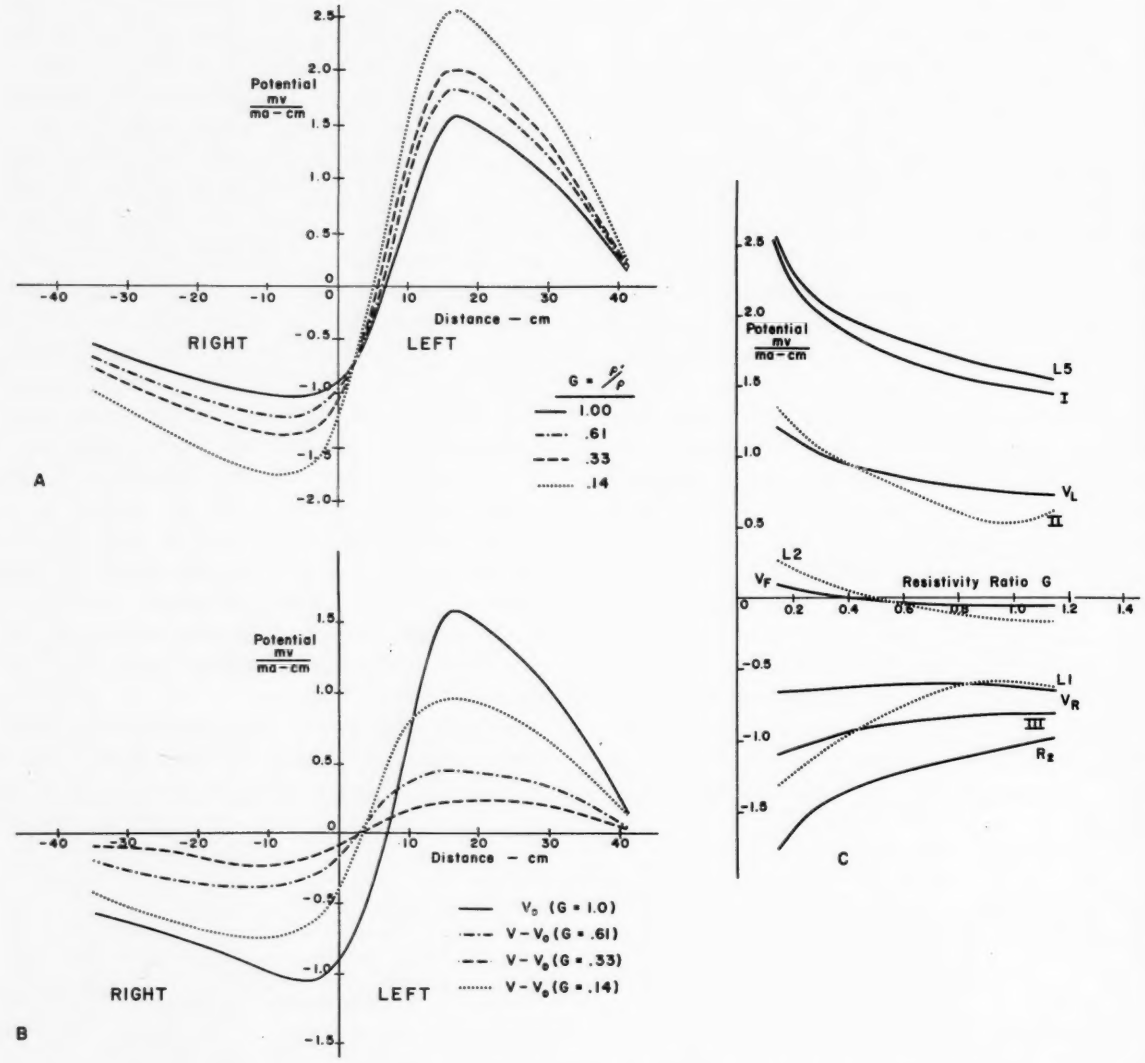

Fig. 2. Tank potentials as a function of the ratio of the resistivities of the bladder and tank fluids, for a radial dipole. *A* shows the potential around the tank at the level of the dipole. −40 and +40 cm. correspond to the center of the back, and 0 cm. to the front midline. The curves in *B* show the *difference* between the distributions for the homogeneous case (G = 1.0) and the distributions when fluids of lower resistivity are in the bladder. Part *C* shows the variation of the limb leads and three wall leads. Lower bladder-fluid resistivity produces a general increase in potentials.

electrode distance of 1.1 cm.; in the latter groups of experiments (with 1960 dates) a new dipole was utilized which consisted of two silver wires, 5 mm. in length and 0.76 mm. in diameter, separated by a distance of 2.76 mm. between the two near edges.

1. Fixed dipole with varying resistivity ratios. In the first series of experiments the position of the dipole was fixed for each experiment, and measurements were made with the bladder filled with fluids of various resistivities. Experiments were performed with the dipole fixed radially (90°), tangentially (0°), or at an intermediate angle relative to the bladder wall (Table I). The distribution of potential around the tank for each fluid was plotted.

In the experiments with tangential dipoles the dipole center could be placed adjacent to the bladder wall. When the dipole was arranged radially or at intermediate angles, the dipole center had to be 4-5 mm. away from the bladder wall because of the size of the dipole.

Results obtained in an experiment using a radial dipole and fluids of four different resistivities are shown in Fig. 2. The resis-

tivities are expressed in terms of the parameter G, which is equal to the ratio of the resistivity of the fluid in the bladder to the resistivity of the tank fluid. In another experiment a tangential dipole used in conjunction with solutions of five different resistivities gave the results shown in Fig. 3. Dipoles with intermediate angles (Fig. 4) gave curves intermediate to those shown in Figs. 2 and 3.

The question arises as to whether it is desirable to show the effect of different bladder-fluid resistivities on the distribution of the wall potentials by plotting for each point the ratio of the potential obtained with the low-resistance fluid to that obtained with the high-resistance fluid, the latter corresponding to a homogeneous medium. In some cases this was not practical since, if the curves under comparison do not have the same zero-potential points on the wall, i.e., if there is a shift in the null axis, the ratio must have the values of zero and infinity at these two points. An alternative way to express the effect is in terms of the change in potential at each point. Such "incremental" curves do not go to infinity at any point. Furthermore, calculation in terms of ratios may create a false impression when small potential values are involved. For example, if there is a change in the potential from 0.02 to

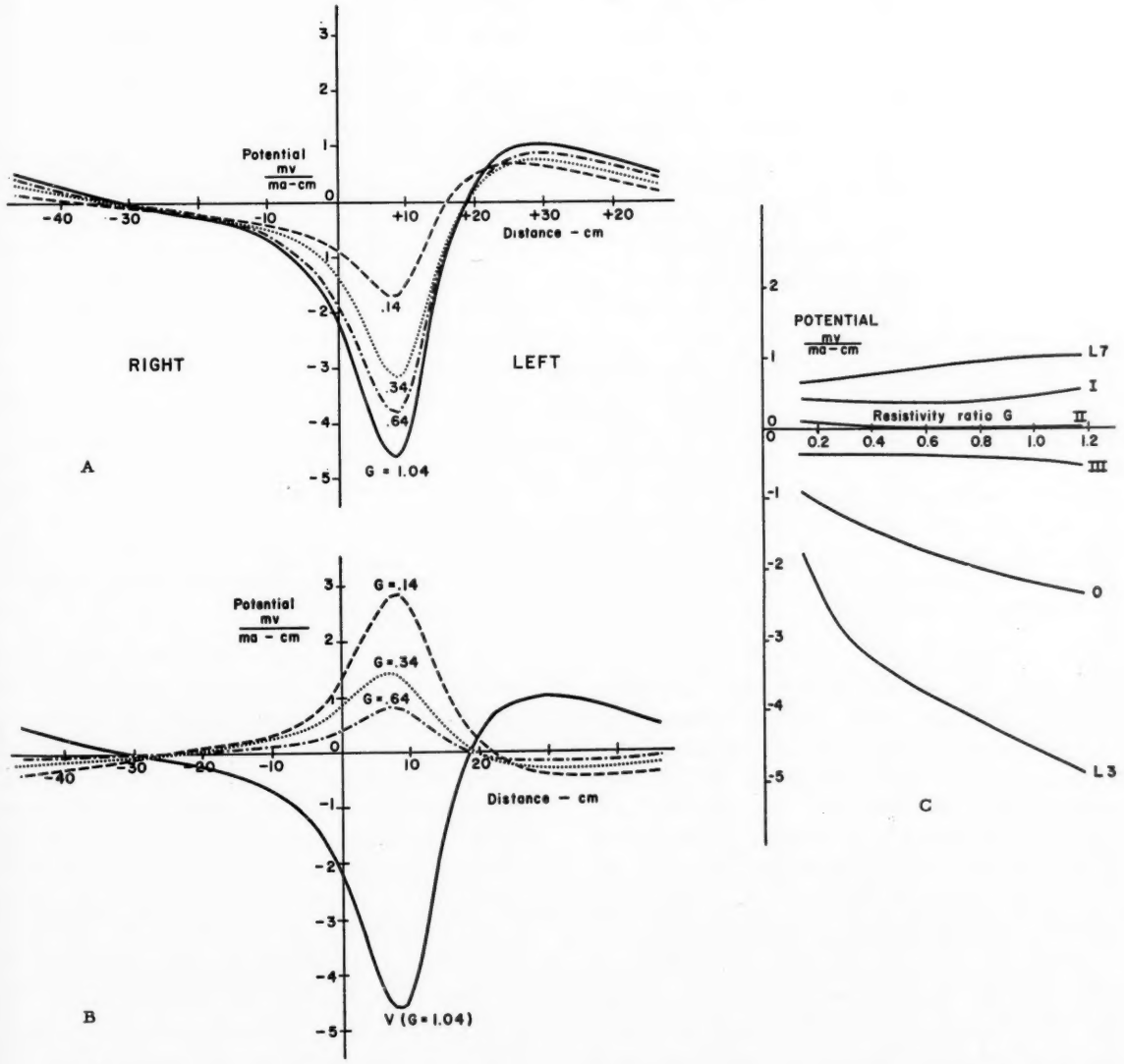

Fig. 3. Tank potentials as a function of resistivity ratio, for a tangential dipole. *A* shows the actual circumferential distributions, and *B* shows the potential-difference curves. *C* shows the variation in potential of the bipolar limb leads and three wall points. Lower values of G produce a general decrease in potentials.

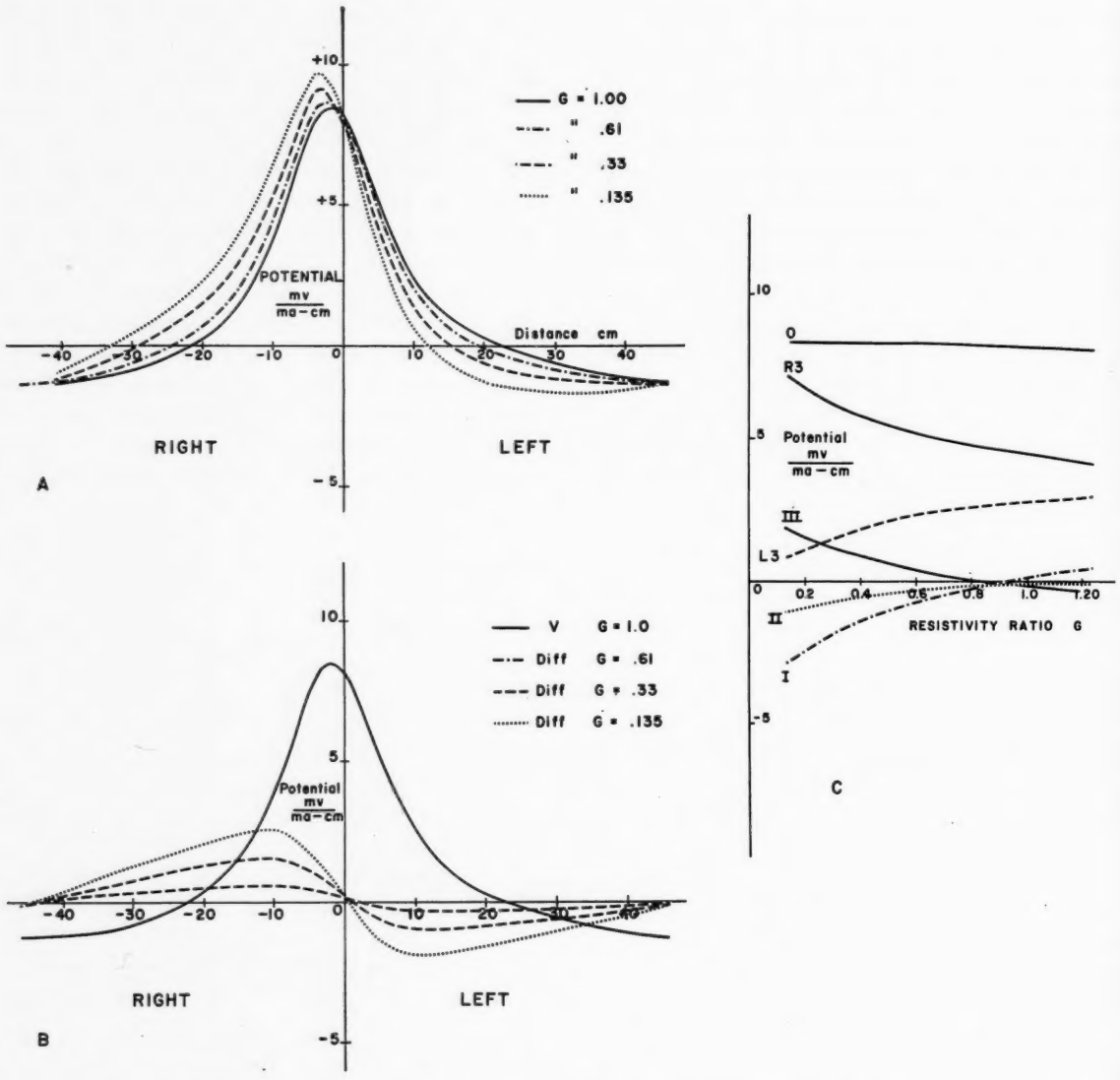

Fig. *4.* Tank potentials as a function of resistivity ratio for a dipole at an angle of 45° with the bladder wall. As G is lowered, the potentials increase in some regions and decrease in others.

0.04 mv., this would correspond to a ratio of 2.0. The difference between these potentials, on the other hand, is 0.02 mv., a fact which may be given its proper perspective. In addition, the incremental curve gives the actual change in millivolts produced by the experiment and can be expressed analytically as the difference between two distributions of potential.

Plots were made showing the difference between the potential-distribution curves for the high-resistivity fluid (representing the case of a homogeneous medium) and those for the fluids of lower resistivity used. These are shown in Figs. 2,*B*, 3,*B*, and 4,*B*. In these figures the actual distributions of potential for the homogeneous cases are also plotted, for purposes of comparison. The other curves then show the potential which must be added to obtain the actual potential for the lower-bladder-fluid-resistivity experiments. In addition, curves were plotted showing some of the wall and limb potentials as a function of the resistivity ratio G, as shown in Figs. 2,*C*, 3,*C*, and 4,*C*.

With the dipole arranged radially it is evident (Fig. 2) that the magnitude of the wall potentials became greater as the resistance of the bladder fluid was lowered (smaller values of G). The magnitude of the limb-lead potentials was also increased, but the calculated Einthoven angle changed

only from +5° to −4°. In the wall-potential distributions there is a common or crossover point, at which the potential is the same for all values of resistivity ratio. This point is located about 3 cm. to the left of the center line. This point does not coincide with the intercept of the transverse axis with the wall, since this is at 5.5 to 6.9 cm. to the left of the center line, depending on G. The significance of this point, if any, is not known.

With tangential dipoles the potential-distribution curves (Fig. 3,*A*) also show the expected results. As the resistivity of the bladder fluid was decreased, the magnitudes of the wall potentials were generally decreased, a change opposite to that observed with a radial dipole. Again, a crossover point exists. In the experiment shown in Fig. 3,*A* this point is at 23 cm., which coincides with the lateral center of the tank. In this experiment the potential of the limb leads changed very little. These potentials were small, since the limb leads in this case were near the dipole null axis. In another experiment (Jan. 23, 1959), all the lead potentials were decreased, whereas the Einthoven angle changed only by 8°.

Fig. 3 shows that the potentials were *increased* by the low-resistivity fluid over a small region on the left side. Similarly, with the dipole oriented radially the potentials measured at the wall a little to the left of the midline were decreased by low-resistance fluids. Both these observations were restricted to small areas and are opposite to the general trend of the changes observed in all other regions.

With dipoles at an angle of 45° to the bladder wall (Fig. 4), the magnitude of the maximum negative potential increased as the bladder-fluid resistivity was lowered, but the magnitude of the maximum positive potential decreased. Thus, the 45° dipole gave results intermediate between the radial and tangential dipoles. The difference curves show that potentials were made more negative on the left side and more positive on the right side. The potential-difference curves show this effect very clearly. The value of α_F was not computed for this case since the dipole was normal to the frontal plane.

With the dipole at 30° the results were similar to those obtained at 45° but the changes were less marked. In this case the difference curve also showed that, as the resistivity of the bladder fluid was lowered, the potentials became more negative over part of the wall and more positive over the remainder.

Tests with the bladder out of the tank gave values which were practically identical to those obtained when the same fluid was used in the bladder and tank (G = 1.00). Slight differences of the order of 1 per cent were observed, and these might have been due to the possible lower resistivity of the bladder tissue itself.

2. Dipole at various distances. In the second series of experiments (Table I) the bladder-fluid resistivity was maintained

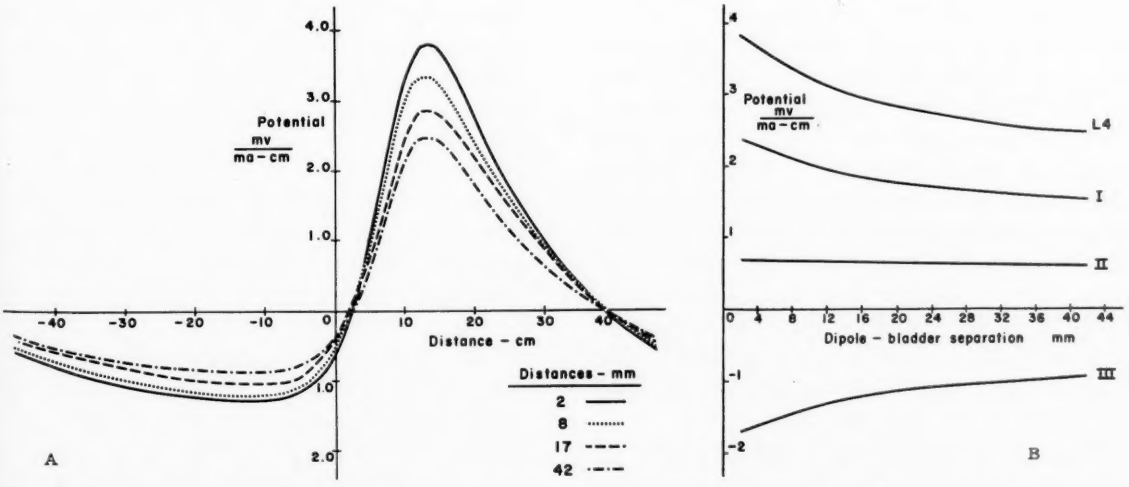

Fig. 5. Potentials as a function of the distance between a radial dipole and the bladder wall. The ratio of bladder-fluid resistivity to tank-fluid resistivity is 0.15.

constant at 140 to 150 ohm-cm., corresponding to an outside-to-inside ratio of resistivities of 6 to 7. Measurements were made with the dipole at various distances from the bladder wall, ranging from 0.2 to 4 cm. This would simulate the condition in the heart when the excitation wave travels from the endocardial to the epicardial layers. In practice, the dipole was kept stationary in the tank, and the bladder was moved relative to the dipole. Thus, the bladder-dipole distance was changed while the dipole position and its orientation relative to the tank wall remained constant. This was done in order to avoid the field changes which would result from movement of the dipole alone.

Results from a representative experiment with a radial dipole at eight different distances are shown in Fig. 5. With a radial dipole the potentials were generally increased in magnitude as the bladder was brought closer to the dipole (Fig. 5,*A*). A separate graph was made of the variation of the peak potential on the left side and the bipolar limb leads as a function of distance between bladder and dipole (Fig. 5,*B*). For the first centimeter the slope of the peak-potential curve is essentially constant. After this the slope gradually becomes smaller, so that the same increment in separation has less effect at greater distances than when the dipole is closer to the bladder. The limb-lead potentials increased by varying amounts as the bladder was brought closer to the radial dipole, although Lead II remained constant. The Einthoven angle changed only by 7°, however.

Tangential dipoles resulted in opposite changes. As the bladder was brought closer to the dipole, the magnitude of the potentials decreased. A graph of the peak potential as a function of dipole-bladder separation shows that in this case also the slope is constant for the first centimeter, and that after this the rate of change decreased. Similarly, as the bladder was brought closer to the dipole, all limb-lead potentials decreased. In Experiment Jan. 9, 1960B, the peak wall potential dropped from 2.1 to 1.1 mv./ma.-cm.

Dipoles at intermediate angles produced opposite changes at different measuring points. With a 45° dipole (Experiment Feb. 3, 1960), bringing the bladder close to the dipole increased the potentials over the right side to the right of a point 7 cm. from the center line, and over the left side from a point 6 cm. to the left of the center line. Between these two points, at the front center region of the tank, the potentials were made more negative. In addition, at such intermediate dipole angles there was a greater shift of the null points than occurred with strictly radial or tangential dipoles. Also, the slope of the maximum-potential curve was not constant over the first centimeter. However, in a study of the effect of distance the bladder was displaced radially from the dipole, so that the relative angle at greater distances may have been altered. The changes in the limb leads were as follows: V_L, 0.22 to 0.76; V_R, − 0.28 to −0.80; V_F, 0.16 to 0.15; I, 0.50 to 1.57; II, 0.44 to 0.95; III, −0.07 to −0.62 (all values in millivolts per milliampere-centimeters). The first value given is for the bladder removed completely from the tank. The second value in each case is for the dipole 2 mm. away from the bladder. α_F changed from 23° to 7°, and since the correct value was 0°, the effect of the low-resistance fluid in this experiment was apparently to offset the inherent error in the Einthoven-triangle method.

In the last experiment shown in Table I the dipole made an angle of 30° with the horizontal plane as well as an angle of 60° with the frontal plane. As the bladder was moved away from the dipole in a horizontal line, the angle between the dipole axis and the bladder wall changed considerably. Comparing only the potentials with the dipole out of the tank with those obtained when the dipole was nearest the bladder, we found that at the center and on the right side the potentials increased in magnitude. The electrode at the center of the front of the tank, for example, changed from −0.5 to −2.4 mv./ma.-cm. The electrode 3 cm. to the left of the center line changed from +0.6 to −1.4. The next electrode changed from +1.8 to 0.9 mv./ma.-cm. This amounted to a decrease in positive magnitude, but was a change in the negative direction similar to that of the leads farther to the right. The electrode 9 cm. to the left decreased only by 0.06, and the next electrode increased from

+1.68 to +1.95 mv./ma.-cm. Leads II and III both increased, from +1.04 to +2.06 and from +0.34 to +1.17, respectively. Lead I changed less, from +0.70 to +0.90. The projected angle α_F changed from 49° to 64°. Although the dipole made an angle α of only 30° with the horizontal plane, the angle between the projection of the vector on the frontal plane with the +X axis, α_F, is different because the vector is not in the frontal plane. The projected vector, α_F, which is found in the Einthoven triangle system, is given[9] by

$$\tan \alpha_F = \frac{\tan \alpha}{\cos \beta} \qquad (1)$$

From this, with $\beta = 60°$, the value of α_F is 49°. In this experiment, therefore, the Einthoven method gave the correct value for α_F in the homogeneous case, and the effect of the bladder was to cause an incorrect value as calculated from the measured limb potentials.

Discussion

The results clearly confirm the theoretical conclusions[9,10] that the effect of a highly conducting medium on an adjacent dipole is to enhance the potentials due to radial dipoles, to diminish those due to tangential dipoles, and to cause an increase or decrease in potential at different field points if the dipole angle is intermediate. They also show that the magnitude of the effect depends on the distance of the dipole center from the conducting mass. The significance of these results in electrocardiology depends, therefore, on the time course of the activation of the heart, i.e., the direction and position of the effective dipoles relative to the cavities.

It is generally agreed that atrial depolarization begins with impulse formation in the sinoatrial node which spreads as a wave through both atria in the direction of the atrioventricular node. This depolarization wave front is relatively unopposed and, for the most part, is longitudinal with respect to the atrial cavities. This spread of excitation is the counterpart of an experimental tangential dipole for any point in time. The P waves must be substantially reduced by the shunting action of the blood. With hypertrophy of the atrial wall, one might expect the excitation wave to assume a more oblique or radial angle with respect to the atrial cavity. This would then represent an experimental dipole with a more radial orientation, and the surface electrocardiogram would record a P wave of increased voltage.

Ventricular depolarization is, of course, much more complex. It has been stated by several authors[11-14] that the initial excitation begins at the termination of the left bundle on the left side of the septum. From this point there is a rapid tangential spread through the endocardial layers, terminating in the posterior wall of the left ventricle at the base of the heart. Subsequent activation of the myocardium is apparently in a transmural direction, even though the time sequence of activation is from apex to base. It has been stated that in the human ventricle the endocardial layers seem electrically silent in respect to the formation of the R wave in the electrocardiogram.[15] The only deflection these investigators were able to record from the endocardial musculature, consisting of one third to one half of the thickness of the left ventricle, was a QS deflection. Perhaps pertinent to these observations is the tangential nature of endocardial excitation and its proximity to the blood-filled cavity. Surface potentials as represented by R-wave deflections may be significantly reduced. As the spread of depolarization shifts to that represented by a radial dipole, that is to say, from endocardium to epicardium, the ECG components should be increased. As the excitation proceeds toward the epicardium, the relative increase would be less, because of the increasing distance from the cavity. The final apex-to-base epicardial vector on the left ventricle would not be changed greatly. Potentials due to effective dipoles spreading from the endocardium at an oblique angle with the cavity wall would be enhanced at some regions of the body and diminished at others.

If one considers the individual dipole components of excitation, rather than the over-all resultant, the picture becomes still more complicated. If radial and tangential or intermediate dipoles existed fairly close together, the contribution of each to the summation would vary. In either case the observed magnitude and direction of the

heart vectors as determined from surface measurements would be different from the true values.

The data show that if the ratio of the resistivity of the myocardial tissue to that of blood is as high as only 4 or 5, the effect of the intracardiac blood on adjacent dipoles must be significant. If the resistivity of the external medium surrounding the heart is still higher, the effect will be enhanced.

Summary

Perfused dog bladders to simulate the intracardiac blood mass were placed in an electrolytic tank in the shape of an elliptical cylinder. An artificial dipole was placed adjacent to the preparation, and wall and limb potentials were measured. Measurements were made with the dipole axis tangential, radial, or at intermediate angles to the bladder wall. In one group of experiments the leads were measured for ratios of bladder fluid to tank fluid of from about 0.14 to 1.20. In the second series of experiments the ratio was kept constant at 0.15, and field potentials were measured as a function of the distance between the dipole and the bladder. The results show that the contribution of a dipole component to the potential at a given electrode depends on the ratio of the resistivity of the blood to the resistivity of myocardial and thorax tissue, the distance of the dipole from the cavity, its direction relative to the cavity wall, as well as on the orientation of the dipole with respect to the electrode.

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An orthogonal lead system for clinical electrocardiography

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Einthoven, in his early investigations of the electrocardiogram, was concerned with the influence of the orientation of the heart on the form of the complexes. His interest in this relationship led to the introduction of the concepts of the manifest vector and the Einthoven triangle. These concepts are two dimensional in character, and apply to the frontal plane. Despite this limitation, they have proved to be so useful that they are routinely employed in electrocardiography today.

The value of Einthoven's approach has been so evident that the possibility of extending it to include all three components of the manifest vector has been under consideration for many years. There are several reasons why the early research with this objective has not culminated in clinical application. The Einthoven triangle itself had, for many years, no clearly demonstrable scientific basis. This basis has since been provided by the concept of the lead vector introduced by Burger and van Milaan. Another problem has been that of obtaining the sagittal component of the heart vector from potentials induced in electrodes on the chest, close to the heart. The recently developed "lead field" concept has shown that the proximity effects can be suppressed through the use of several electrodes whose potentials are averaged. Still another obstacle has been the difficulty of determining the electrical axis in three dimensions without burdening the clinician with calculations of inordinate mathematical complexity. An answer to this problem is the use of "resolvers," electronic instruments introduced by Schmitt[1] and studied by several other investigators.[2-5] It has been shown[9] that the approximate mean electrical axis of the "QRS" and "T" complexes can easily be determined with these devices. These instruments can be built as compact and reliable units well adapted to the clinic.[6]

Because of these relatively recent developments, it is now possible to determine the electrical axis of the heart in the clinic in three rather than two dimensions. All that is required is a lead system which provides the three components of the heart vector.

A great number of such orthogonal lead systems have been proposed, each with merits and deficiencies of its own. It is beyond the scope of this article to review each of them. In our opinion, even the best systems, such as Schmitt's[7] and Frank's,[8] do not strike the optimum balance between accuracy and simplicity.

In this report an orthogonal system is described which is intended to satisfy clinical requirements. It is designed specifi-

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This investigation was supported by Research Grant H-3949 from the National Heart Institute, U. S. Public Health Service, and by a research grant from the Onondaga County Heart Association, Syracuse, N. Y.
Received for publication Dec. 27, 1960.

cally for determining the electrical axis of the heart on a routine clinical basis. It represents a carefully drawn compromise between the simultaneous need to maximize accuracy and to minimize complexity. The system has been subjected to quantitative studies aimed at finding the optimal configurations and number of electrodes, the optimal electrode spacing, the relative sensitivities of the leads, the influence of variations in body shape, the effect of the electrical heterogeneity of the trunk, and the error resulting from misplacement of the electrodes.

The report is divided into two parts. Part I describes the system in detail and is intended for the clinician who desires detailed instructions as to the placement of the electrodes and connections to the electrocardiograph. Part II outlines the various studies of the system which have been made and is intended primarily for the research worker who is interested in the concepts and measurements on which it is based.

Part I. The axial system

Lead connections for human subjects. Fig. 1 shows a diagrammatic sketch of the location of the lead electrodes and the connections between them. The photographs of a human subject in Fig. 2 also demonstrate the position of the electrodes. The electrodes are paired together and form three leads, each electrode group symmetrically arranged about an axis which passes through the center of the heart. The axes thus formed are oriented in the longitudinal (head to toe), transverse (left to right), and sagittal (front to back) directions, respectively. It is because of these three mutually perpendicular axes that the electrode configuration is referred to as an "axial" lead system. The reference directions for all leads are taken so as to give predominantly upward deflections with normal subjects.

A. LONGITUDINAL LEAD (Y AXIS). The longitudinal lead is taken between an electrode on the left leg and a second electrode attached to the left side of the neck.* The connections to the amplifier are such that an upward deflection will occur when the leg is electrically positive relative to the neck.

B. SAGITTAL LEAD (Z AXIS). The sagittal lead is taken between three electrodes on the chest and a fourth electrode on the back. The potential of the chest electrodes is averaged by means of three 100,000-ohm resistors. Precision resistors (± 1 per cent) should be used.

The chest electrodes form an equilateral triangle so oriented that its base is nearest the subject's feet. For subjects whose height lies in the range of 170 ± 30 cm. (4 feet 7 inches to 6 feet 7 inches) the electrode centers are located *6 cm.* from the center of the triangle. For children and small adults it is desirable to change spacing of the chest electrodes. The spacing in their case should be directly proportional to height. For example, for a child of one half the reference height of 170 cm., i.e., 85 cm., the spacing between the center of the electrodes and the center of the triangle should be 3 cm. The back electrode lies directly behind the center of the chest triangle.

The center of the triangle should, in theory, be directly above the center of gravity of the ventricles. In practice, the exact location of this point is exceedingly difficult if not impossible to determine. However, anatomic, radiologic, and electrocardiographic data indicate that the point on the chest in the fifth intercostal space 2 cm. to the left of the sternal margin is approximately over the center of gravity of the ventricles. The center of the triangle should be placed at this point except in such cases as dextrocardia, wherein the center of the heart obviously differs substantially from the position specified above.

The sagittal lead is connected so that an upward deflection occurs when the back is electrically positive relative to the chest.

C. TRANSVERSE LEAD (X AXIS). The transverse lead is taken between two electrodes on the left side and a third on the right. The potential of the left electrodes is averaged with two 66,000-ohm resistors. (Any resistance value between 60,000 and 70,000 ohms is satisfactory, but it is necessary that the resistors be equal.) Precision resistors (± 1 per cent) should be used. The right electrode lies at the same longitudinal

*In dextrocardia the electrodes should be placed on the right leg and right neck, rather than the left.

level as the center of the electrode triangle on the chest. It is located on the right side, one third of the way from the chest to the back. For example, if the depth of the chest is 18 cm., the electrode should be located 6 cm. from the plane of the anterior chest wall and 12 cm. from the plane of the back. The electrodes on the left side should also be located one third of the way toward the back at longitudinal levels 5.5 cm. above and below the level of the center of the chest triangle. The electrode spacing is therefore 11 cm. If the spacing of the chest electrodes is changed, the spacing of these side electrodes should be changed by the same factor. For example, if the chest electrodes are located 3 cm. rather than 6 cm. from the center of the triangle, then the side electrodes should be located 2.75 cm. rather than 5.5 cm. above and below the heart level.

The transverse lead is connected to the amplifier so that an upward deflection occurs when the left side is electrically positive relative to the right.

Lead connections for dogs. The lead system proposed for dogs is shown diagrammatically in Fig. 3. It is identical to the one

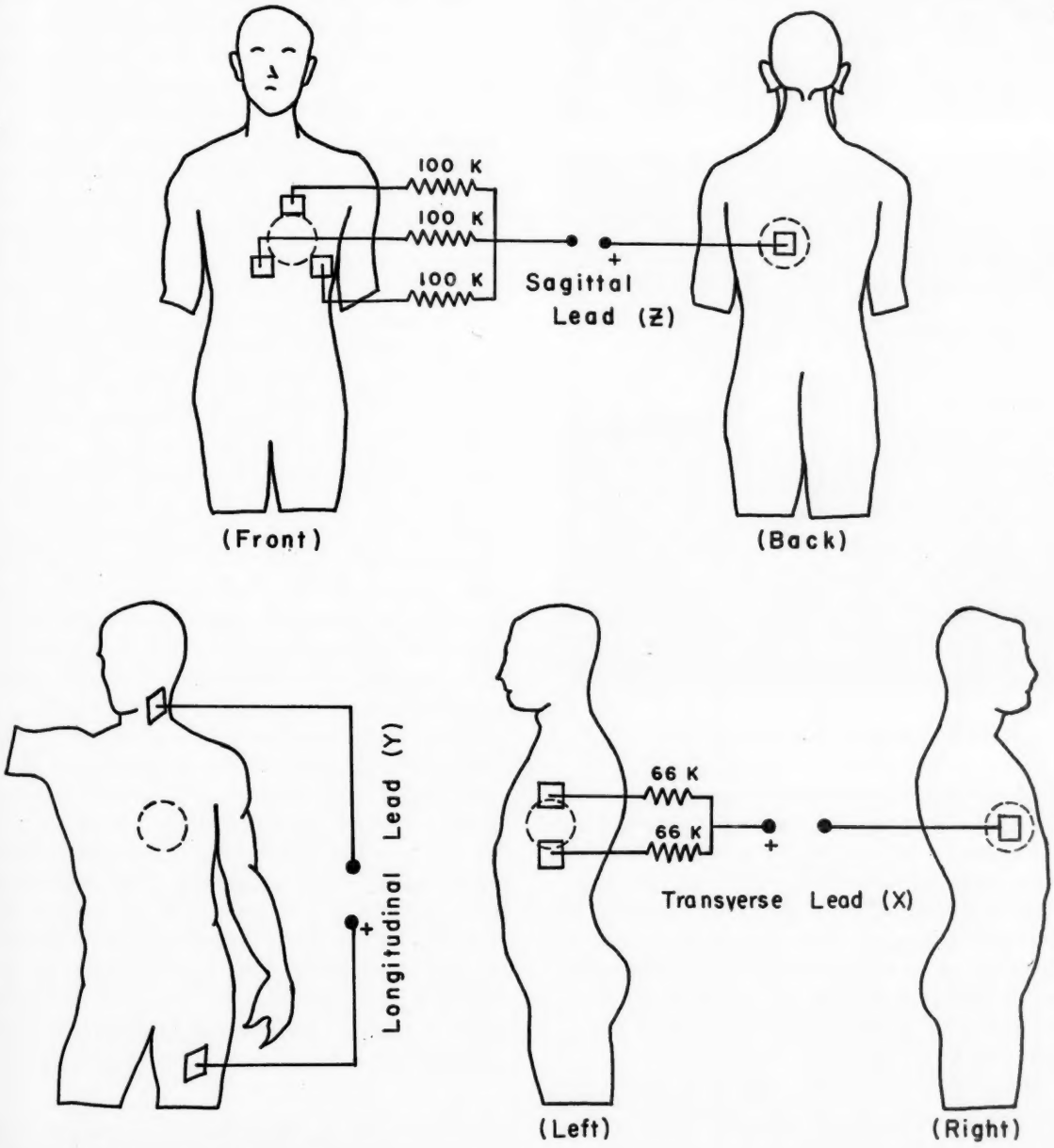

Fig. *1.* Location of "axial" lead electrodes.

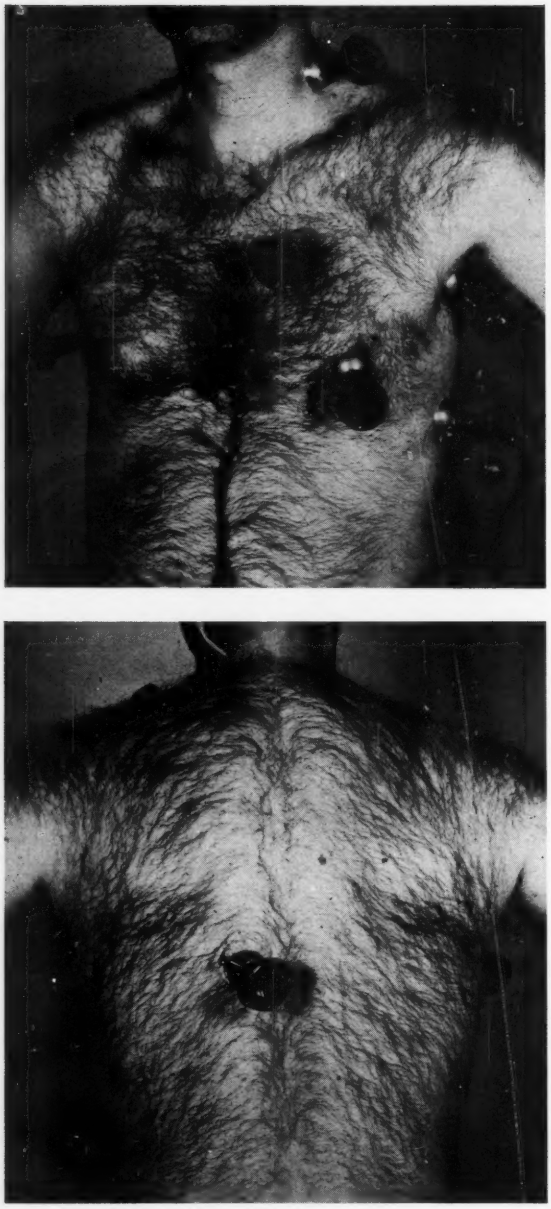

Fig. 2. Subject with electrodes in position.

used for human subjects except that there are two electrodes on the right side rather than one. The relatively narrow chest of dogs and the central location of the dog's heart required this change. The spacing of the electrodes on the sides and the chest remains as in the system for human subjects. The center of the triangle formed by the three chest electrodes is placed directly over the sternum.

Amplifier sensitivity. The voltages from all of the three leads should be recorded with the same calibration, i.e., some specified deflection per millivolt.

Electrodes and electrode placement. Suction electrodes have proved to be quite adequate for this lead system, and are recommended for all electrode sites except those of the left and right legs, left neck, and back. (The right leg electrode is the "ground.") Strap electrodes are more suitable for the legs. Either a suction or a strap electrode can be used on the left neck. The back electrode can be a flat plate on a flat rod, held in place by body pressure, or a suction electrode.*

Time can be saved in placing the electrodes through the use of the Lucite template shown in Fig. 4. An efficient procedure for electrode placement is the following: (a) Determine and mark with a crayon the point in the fifth intercostal space 2 cm. to the left of the left sternal margin. (b) Center the chest template on this point with its base toward the subject's feet, and mark the subject with a crayon through the three holes in the template. (c) Place the template on the left side and mark points one third of the way from chest to back at the longitudinal levels, 5.5 cm. above and below the center of the chest electrodes. (d) Place suction electrodes over the five marks on the left side and chest. Place a suction electrode on the right side one third of the way from chest to back at the same longitudinal level as the center of the chest triangle. Place the electrode on the back directly behind the center of the chest triangle. Place a suction or strap electrode on the left neck. (e) Place strap electrodes on the two legs. (f) Connect electrodes to the box containing the averaging resistors.

Cables and connector boxes. Fig. 5 shows the wiring diagram for a one-channel electrocardiograph. The wiring diagram for a three-channel electrocardiograph is identical, except that the switch and the 33,000-ohm resistor are removed. The shielding and grounding arrangements shown are intended to minimize the possibility of 60-cycle interference. The cables must be securely anchored to the connector box in such a fashion that frequent flexing of the cables does not lead to open or short circuits.

*It is recommended that the suction electrode on the back be of the relatively flat type, with a long tube between the electrode and the suction bulb.

The extra 33,000-ohm resistor shown in the longitudinal lead in Fig. 5 prevents a slight increase in sensitivity occurring when this lead is taken with an electrocardiograph having a relatively low input resistance (1,500,000 ohms or less). The resistor is not needed with electrocardiographs having an input resistance greater than this value.

If desired, the averaging resistors for the electrodes on the chest and the left side can be placed near the end of the cables rather than in the connector box. If this is done, the resistors must be shielded and great care taken to insure that flexing of the cables does not cause open or short circuits.

Part II. Design of the system

The selection of an orthogonal lead system for use in electrocardiography is a problem in design rather than a subject for scientific investigation. There is no unique answer. In fact, there is an infinite number of solutions, none subject to exact analysis, and each of which represents an attempt to obtain some sort of optimal compromise between a variety of conflicting requirements. The "axial" lead system described here represents an attempt to achieve such an optimum.

Data for the design of the system have been obtained from three sources: a homogeneous model of the human body, mathematical models, and live human subjects. Measurements from live subjects sometimes differed significantly from those obtained with homogeneous models. The relatively low resistance of the surface musculature appears to account for most of these differences.

The configuration adopted for the electrodes has several desirable features. The electrodes on each of the six sides of the body form three orthogonal axes. If the position of the heart is known, they can easily be located so that these axes pass through the heart center. An advantage to the use of multiple electrodes on the left side and chest (areas close to the heart) is that they tend to eliminate "proximity" effects. Use of multiple electrodes also makes the lead less sensitive to errors in electrode position. This point is illustrated schematically in Fig. 6.

That proximity effects are indeed small was demonstrated by comparing the voltage of these leads with voltages of "ideal" leads composed of many electrodes effectively covering the entire surface of the body. The sagittal "ideal" lead, for example, employed 19 electrodes on the

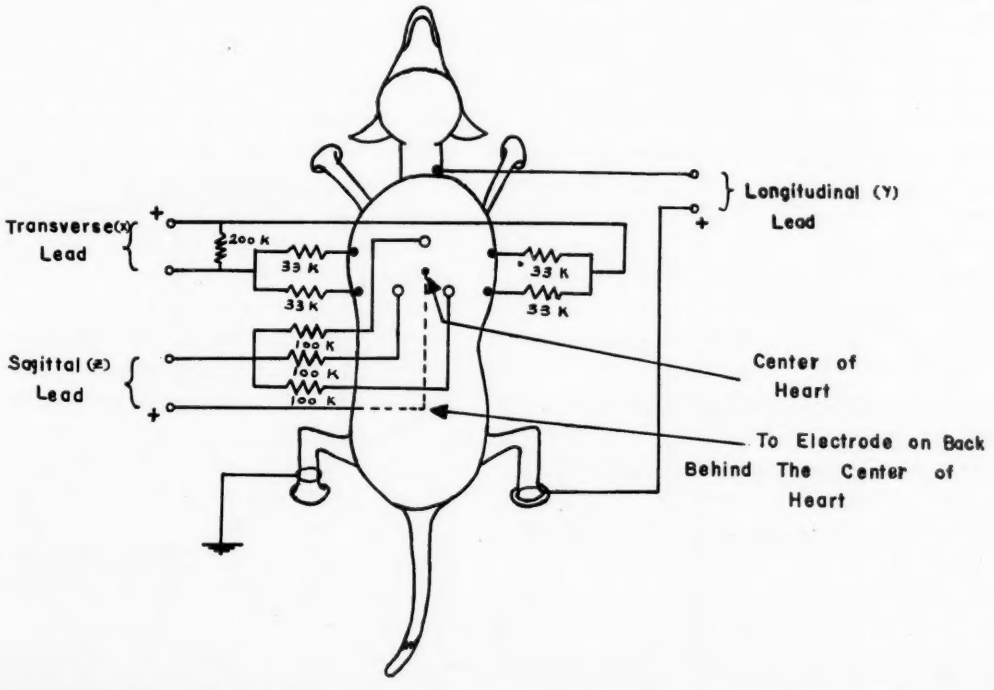

Fig. 3. Location of dog leads.

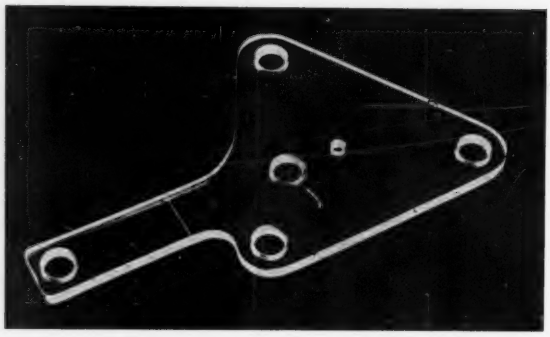

Fig. *4.* Oblique view of template used to mark location of electrodes. The hole in the center of the triangular section is 6 cm. from the holes in the corners of the triangle. The hole at the end of the handle is 11 cm. from its mate which lies just within the triangular area.

chest and stomach and 16 on the back. Eighteen records obtained from six subjects showed that the forms of the voltages in the "axial" and "ideal" leads were so similar as to be effectively indistinguishable. The only important difference noted was one of amplitude.

The spacing of the lead electrodes was established by experiments with the tank model. The spacing chosen gives the most uniform field in the heart region of the tank.

The relative sensitivities of the leads were obtained first with a tank of dimensions and shape similar to those of the average human body. The tank was filled with tap water. The sensitivities of the transverse and longitudinal leads were found to be equal, whereas the sensitivity of the sagittal lead was 20 per cent greater.

A check on this method was made by comparing the relative amplitude of the voltages in the axial and ideal leads. From the known cross-sectional area of the latter the absolute strength of the lead field (amperes per square meter) could be determined, under the assumption that the lead field was uniform. The known relative amplitudes of the axial lead voltages then allowed their lead fields to be estimated in turn. Studies of six subjects indicated that the transverse and sagittal leads have equal sensitivity, whereas that of the longitudinal lead is 25 per cent greater. The difference between this result and that obtained with the model could be attributed to shunting

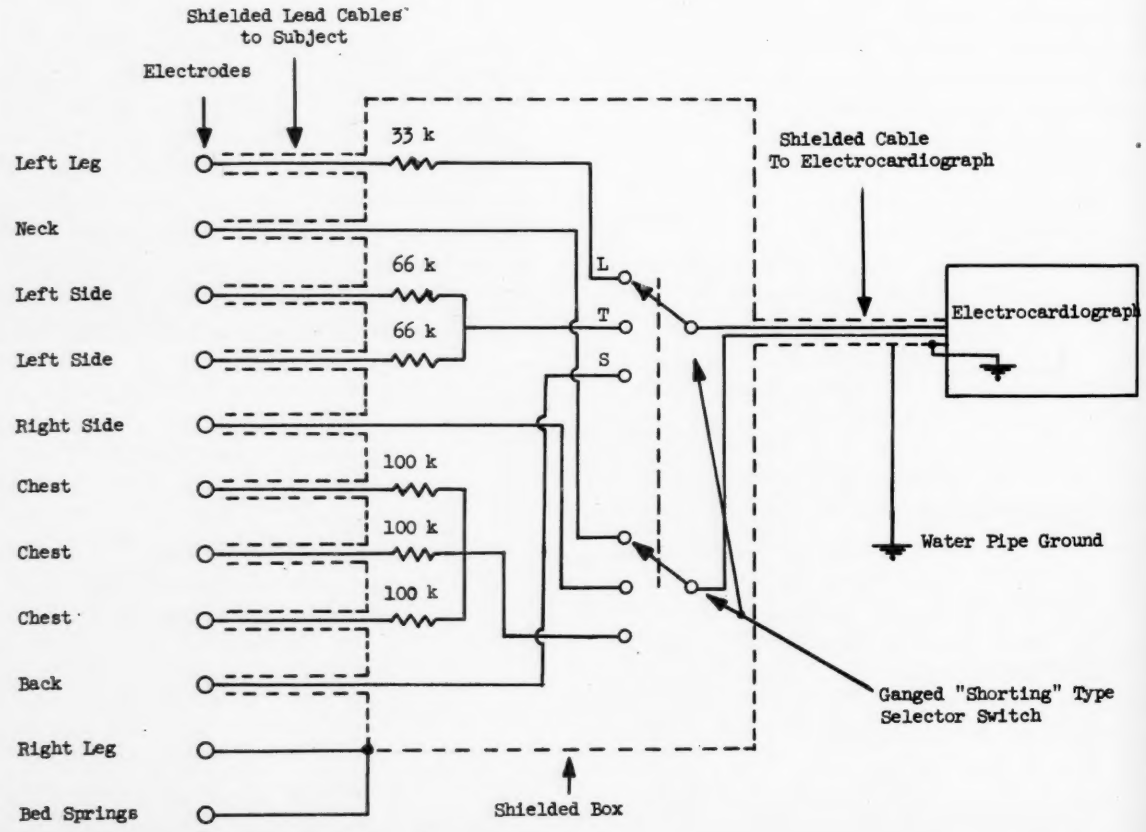

Fig. *5.* Wiring diagrams for single-channel electrocardiograph.

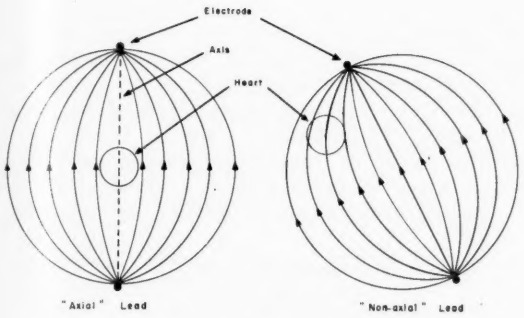

Fig. 6. Lead field of "axial" and "non-axial" leads. Note that the field of the axial type will change considerably less than that of the non-axial type when the relative position of the heart and electrodes is altered.

of the lead field by the low-resistance layer of muscle directly under the skin.

The effect of the relatively low resistance of the heart-blood mass on the sensitivity of the leads was also investigated. Reflections by the chest surface of perturbations of the lead field produce a decrease in the sensitivity of the sagittal lead, and a smaller decrease in the sensitivity of the transverse and longitudinal leads. These changes were estimated mathematically by representing the heart as a homogeneous sphere in an otherwise homogeneous semi-infinite conductor of three times the heart's resistivity. A decrease in the relative sensitivity of the sagittal lead of roughly 5 per cent was computed.

An average figure for the lead sensitivities has been adopted. Accordingly, the sensitivities (and hence weighting factors) of the three leads have been made equal.

The influence of variations in body shape on the sensitivities of the leads was also investigated. A box-shaped tank model with movable glass sides was used for this purpose. These studies showed that significant changes in sensitivity from the average occurred mainly in those subjects who had slender, flat chests. Here the sensitivity of the sagittal lead increased by as much as 30 per cent. The sensitivities of the other leads increased also. The effect is similar to that produced by ventricular enlargement. It does not seem that the changes are, in general, large enough to justify custom tailoring of the leads to each individual subject. Nevertheless, the clinician should be aware of the augmentation of lead voltages which occurs in subjects with long, thin chests.

A study was made to determine whether substantial changes in resistivity within the heart could prevent the axial lead system from compensating for variations in heart orientation. Theoretical analysis indicated that they would not, since the heart's dipole moment, as seen from a remote point, will rotate with a mechanical rotation of the heart. An experimental check of this was made by constructing an assembly whose resistance differed drastically from that of the tap water of the tank model in which the assembly was immersed. A dipole fixed to this assembly was activated for each of six orientations of the structure. The changes in orientation were counteracted by an electrical counterrotation (using the resolver principle) of the voltages induced in the axial leads. Almost perfect compensation was achieved in every case. This demonstrated that differences in resistance of heart muscle and blood, and anisotropy of the muscle, would not prevent the dipole moment of the heart's field from being determined, even though an interpretation of this moment as the vectorial sum of the heart's electromotive forces would be inaccurate.

The sensitivity of the axial lead system to changes in the location of the electrodes was determined by a comparison of voltages induced in two identical leads displaced from one another in a longitudinal direction. In eight normal and nine abnormal subjects a 5-cm. displacement of the axial lead electrodes produced an average difference voltage of 10 and 22 per cent, respectively, of the transverse and sagittal lead voltages. For comparison, the Frank lead system was investigated under identical circumstances, and yielded voltage differences averaging 25 and 33 per cent, respectively, for its transverse and sagittal leads.

These experiments also showed that the smallest changes occurred in the lead voltages as a result of errors in electrode placement when the fifth intercostal space was used as the reference level for the transverse and sagittal leads. This finding is in agreement with anatomic and radiologic data regarding the position of the ventricles.

Conclusion

Although the investigation of the axial lead system is continuing, we believe that enough work has been done to warrant its recommendation to clinicians who have need of a set of orthogonal leads. The studies reported have shown that the axial lead voltages are almost identical in form to those obtained with "ideal" leads using large numbers of electrodes. In addition, they have shown that the system is not unduly sensitive to variations in body shape, or errors in electrode location. All evidence gathered thus far indicates that the system provides a reasonably adequate means of determining the three orthogonal components of the dipole moment of the heart's electrical field.

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The atypical systolic murmur of minute ventricular septal defect and its recognition by amyl nitrite and phenylephrine

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An unusual systolic murmur characteristic of very small ventricular septal defects has been investigated in 12 patients. It is a short, crescendo-decrescendo murmur which terminates well before the second heart sound. Since it resembles an ejection systolic murmur[1,2] and is unaccompanied by abnormal clinical, electrocardiographic, or radiologic signs, ventricular septal defect may escape consideration in the differential diagnosis.

Because no reference is made to this type of murmur in many recent papers on the ventricular septal defect, we thought it worth while to draw attention to it and the methods used in the diagnosis of very small septal defects. Although other authors[3-5] have stated that occasionally the murmur may be short in small septal defects, Leatham[1] was, to our knowledge, the first to suggest that a short murmur confined to early systole may be produced by a defect in the muscular septum. The short duration was attributed to closure of the defect when the ventricle is fully contracted.

It is the thesis of this paper that simple auscultation, aided by amyl nitrite[2] and phenylephrine,[6] is the most sensitive clinical method of diagnosing these defects.

Material and methods

Twelve patients with loud short crescendo-decrescendo murmurs were studied because the response to amyl nitrite and phenylephrine strongly suggested an atypical ventricular septal defect.[2,6] Eight patients were catheterized.

Amyl nitrite was administered to all patients and phenylephrine to most, and the changes in the murmur and heart sounds were always confirmed by recording sound-tracings at fast paper speed according to the techniques previously described.[2,6] The tests were repeated during cardiac catheterization in order to correlate the change in murmur with simultaneously recorded left-sided and right-sided pressures and dye-dilution curves, obtained before and at the peak responses to amyl nitrite and phenylephrine.[7] By this means the change in murmur could be correlated

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Part of the expenses of this work has been defrayed by grants received from the Council for Scientific and Industrial Research and the City Council of Cape Town.
Received for publication Jan. 9, 1961.

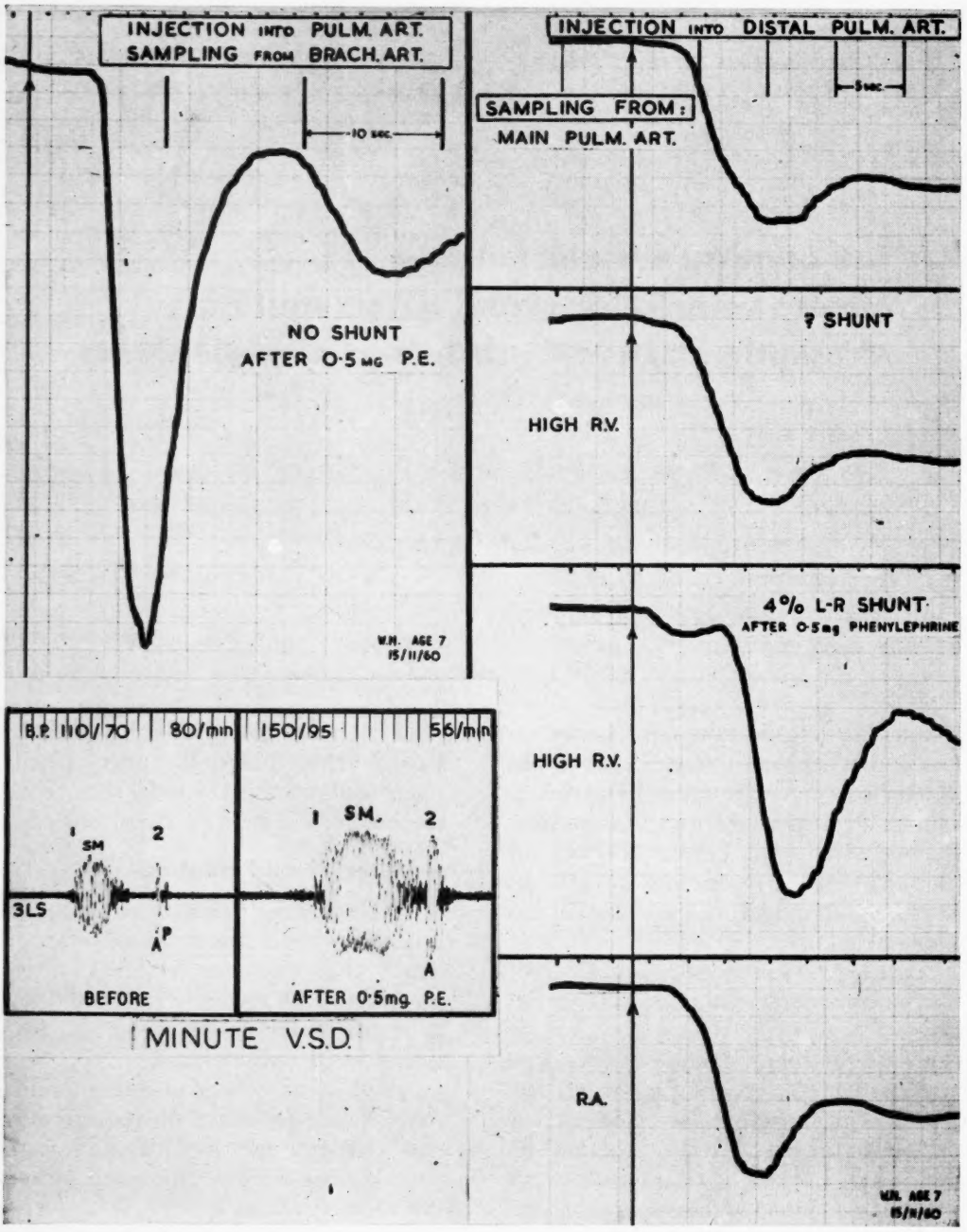

Fig. *1.* Case 5, W. M. Dye-dilution curves and sound-tracings before and after phenylephrine in the smallest ventricular septal defect studied. The dilution curves obtained at the brachial artery after injection of 2.5 mg. of Cardiogreen into the pulmonary artery show no evidence of left-to-right shunt before (*not shown*) and after phenylephrine. But the sound-tracing reveals great intensification and lengthening of the unusually short crescendo-decrescendo murmur, strongly suggesting a small ventricular septal defect. Dye-dilution curves obtained from the right heart after injection of 2.5 mg. of Cardiogreen via a second catheter in the distal pulmonary artery reveal a doubtful left-to-right shunt in the main pulmonary artery and high right ventricle; but only after phenylephrine is the shunt convincingly shown. Note the delayed circulation time caused by phenylephrine. The curve from the right atrium was recorded after phenylephrine had largely worn off; there is no left-to-right shunt at this site. The small dots measure milliliters of blood flow through the densitometer. (The unusual appearance of the murmur after phenylephrine is due to capacitance overloading of the tape recorder by the unexpectedly great intensification.)

with the change in pressure gradient and precentage shunt flow.

The diagnostic procedure used for the detection of small left-to-right shunts was as follows. Routine catheterization was performed, using a Waters cuvette oximeter for direct oximetry of multiple samples of blood taken in rapid succession from various sites in the heart. Dye-dilution curves were recorded at a systemic artery after injection of Cardiogreen into the right side of the heart, using a Norman cuvette densitometer and a Honeywell recorder. The curve was repeated during the peak pressor effect of phenylephrine, which was given with the object of eliciting or accentuating a left-to-right shunt.

The technique employing two venous catheters was used whenever the above-mentioned method failed to detect a shunt. Dye-dilution curves obtained from the proximal pulmonary artery, high and low right ventricle, right atrium, and superior vena cava after the injection of Cardiogreen into the distal pulmonary artery enabled detection of trivial shunts and their localization to the ventricle.[8] Phenylephrine was again used to increase the shunt. The magnitude of the shunt was determined by relating the area of the abnormally early-appearing deflection in the right ventricle to the area of the dilution curve recorded at a systemic artery after injection into the right heart. Two assumptions were made, namely, (1) that the cardiac output did not change between the recording of the venous and arterial dye-dilution curves; and (2) that the area of the systemic arterial curve would not be significantly different from that of the curve recorded in the pulmonary artery after injection into the superior vena cava, in view of the very small shunt.

The phonocatheter was then used to

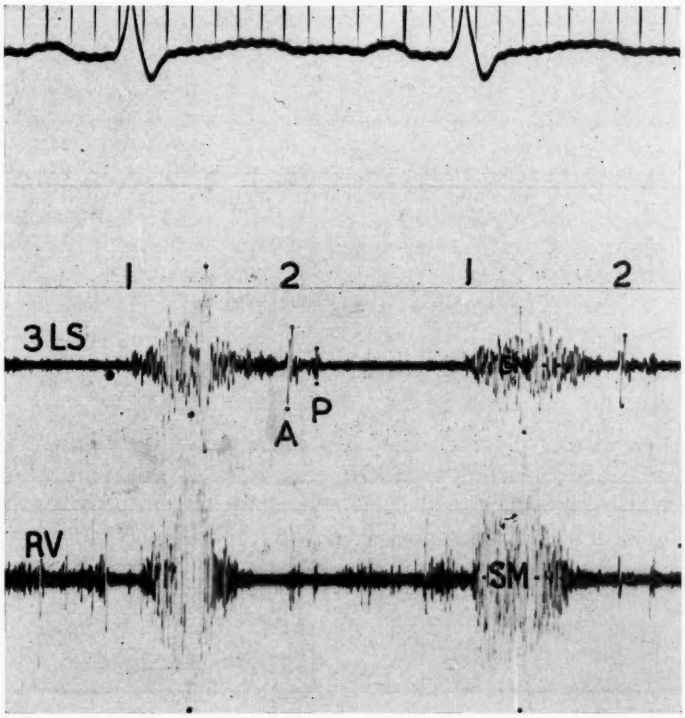

Fig. 2. Case 1, T. A. The synchronously recorded external (*3LS*) and intra-right ventricular (*RV*) sound-recordings reveal short, loud, high-frequency crescendo-decrescendo murmurs of identical shape, proving that the atypical, externally recorded murmur, which appears to be an ejection murmur, is truly representative of the non-pansystolic murmur generated within the right ventricle by a minute septal defect. Amyl nitrite and phenylephrine softened and intensified both murmurs, respectively. There was a softer, lower frequency, physiologic ejection murmur in the pulmonary artery, and no murmur in the right atrium.

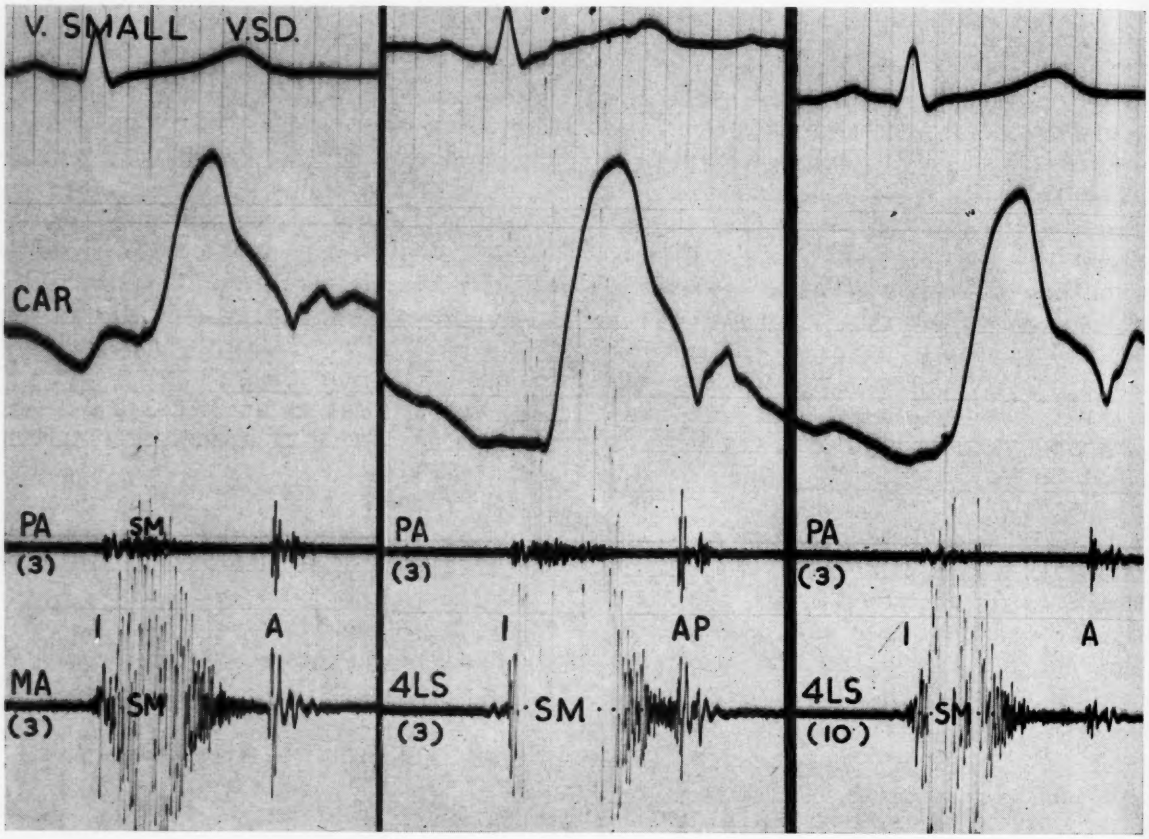

Fig. *3*. Case 4, L.D. The early systolic crescendo-decrescendo murmur of minute ventricular septal defect closely resembles an ejection systolic murmur. The murmur is loudest at the fourth left intercostal space (*4LS*), where a striking decrescendo follows the intense high-frequency murmur which reaches a crescendo in the first quarter of systole. At greater amplification (*3* as compared with *10*), distinct high-frequency, low-amplitude vibrations reach the aortic component (*A*) of the second sound, suggesting a regurgitant systolic murmur despite its diamond shape. The murmur is much softer in the pulmonary area, and splitting of the second sound is normal.

detect the intracardiac murmur according to the technique described by Lewis and associates[9] and elsewhere.[10] Intracardiac and external sound-tracings were simultaneously recorded with the electrocardiogram, and sometimes with intra-arterial and intraventricular pressure pulses, and the influence of amyl nitrite and phenylephrine on these was studied.[11]

Results

In all 12 patients, amyl nitrite softened the early systolic murmur, whereas in all 8 to whom phenylephrine was administered the murmur became much louder and longer. These responses identified the murmur as a left-sided regurgitant murmur, despite its atypical shape.

Of the 8 patients catheterized, only one showed a questionable small rise in oxygen saturation at the right ventricular level, suggesting a left-to-right shunt of about 10 per cent. In the remainder, no shunt was detectable by blood sampling techniques even after phenylephrine. This confirms the limitations of this method even when adequately performed using multiple samples in rapid succession for detecting small left-to-right shunts.[12] All patients had normal right heart and systemic pressures, with no evidence of pulmonary or infundibular stenosis.

In 7 patients, dye-dilution curves were obtained at a systemic artery after injection into the right side of the heart. None of these curves revealed any evidence of a left-to-right shunt, thus confirming the failure of this method to detect small left-to-right shunts.[13] In 6 patients, phenylephrine failed to elicit any detectable shunts by this method (Fig. 1), but in one patient in whom the dilution curve was

recorded from a Norman earpiece densitometer, a clear-cut, small, left-to-right shunt was demonstrated only after phenylephrine.

With regard to the 5 patients studied by the technique employing two venous catheters, very small shunts, which ranged from about 4 to 9 per cent, were demonstrated in all and localized in every case to the right ventricle. In one patient the shunt was so small that the curve obtained from the right ventricle was inconclusive. Nevertheless, a shunt was convincingly demonstrated after phenylephrine had increased the pressure gradient (Fig. 1). The percentage shunt diminished with amyl nitrite, and increased after phenylephrine in all patients. However, the magnitude of the change was slight, as compared with the pronounced changes in intensity of the murmur and in simultaneously recorded pressures (Figs. 1 and 4).

Of the 3 patients studied by the *phonocatheter*, high-frequency murmurs of crescendo-decrescendo shape were recorded within the right ventricle in all. These tracings had a configuration similar to that of the simultaneously recorded external tracing (Fig. 2). However, it was impossible to determine with any certainty whether the defect arose in the membranous or muscular septum. Muscular defects are usually situated at any level in the muscular septum subjacent to the anterior ventricular wall,[14] but occasionally they are found along the posterior wall, and they may be multiple. Hence, the murmur should be picked up anteriorly and inferiorly, but because of difficulty in accurately locating the phonocatheter during fluoroscopy in the anteroposterior view we achieved little success in siting the defect. However, in one patient the murmur was only recorded at the apex of the right ventricle, which strongly suggested a very low and unusually situated defect. This seemed to account for the external murmur being loudest at the mitral area.

Amyl nitrite shortened and softened both the external and intraventricular murmurs, whereas phenylephrine had the reverse effect (see Fig. 4 of Schrire and associates[11]). This established that the murmur within the right ventricle was a left-sided regurgitant murmur even though it had the shape of an ejection type of systolic murmur. Most patients had intrapulmonary ejection systolic murmurs,[11] which is a normal finding.[9,10]

Clinical features

Of the 12 patients, 6 were girls and 6 were boys; they ranged in age from 3 to 15 years. In 4, the murmur was first discovered in early infancy. In the others it was found accidentally, and was the only indication of heart disease. Physical development was normal in all, and none had symptoms referable to the heart. Associated congenital deformities were absent, and anterior bulging of the sternum was not present. A systolic thrill was palpable in only 2 patients. Electrocardiographic and radiologic findings were completely normal in all.

Auscultatory and phonocardiographic findings

The heart sounds were normal in all, but at the site of maximal intensity of the murmur it was difficult to hear the first sound because the murmur commenced with it. Splitting of the second heart sound was never more than 0.03 second during expiration, and increased in the normal manner during inspiration. Ejection sounds were absent. An apical third sound, presumably physiologic, was heard in 2 patients; it was very loud and misleading in one whose murmur was loudest at the mitral area. Mid-diastolic apical flow murmurs were absent in all.

The *systolic murmur* was Grade 3 in intensity in 10, and Grade 2 and Grade 4, respectively, in the other 2 patients. (Intensity was graded from 0 to 6.) The site of maximal intensity was usually sharply localized in the third or fourth intercostal space at the left of the sternal border, but in one patient it was loudest at the mitral area. The murmur was never widely conducted, being particularly loud in a restricted zone and soft elsewhere, tending to radiate toward the apical and pulmonary areas. The same murmur was not heard in the vessels of the neck. In one exceptional patient the murmur was loudest at the mitral area, and was better conducted to the fourth left intercostal space than to the axilla. The murmur had a high-frequency quality in all. Respiration had a variable effect; in 2 patients the

murmur became much softer during inspiration, probably because of a shift of the heart away from the chest wall. In another it became more pansystolic during inspiration.

The most unusual but characteristic feature was the shortness of the murmur. Commencing immediately with the first sound, it reached a striking crescendo by the first third of systole, and then softened rapidly, resulting in an early diamond-shaped murmur confined to early systole. This, together with the apparent cessation well before the aortic second sound, caused it to resemble closely an ejection systolic murmur (Fig. 3). However, the sound-tracing, when recorded with increased amplification, usually provided evidence that the murmur was, in fact, a regurgitant type of murmur. The presence of low-amplitude, high-frequency, inaudible vibrations in the latter quarter of systole extending into the aortic second sound suggested that regurgitant flow was, in fact, continuing throughout systole (Fig. 3).

Response to amyl nitrite and phenylephrine

The response to amyl nitrite and phenylephrine was the most important feature in the diagnosis, since it at once excluded ejection systolic murmurs.[2,6] Whereas ejection systolic murmurs intensify after amyl nitrite and change very little with phenylephrine, this murmur behaves like a left-sided regurgitant murmur.

In all 12 patients the murmur softened greatly and, usually but not always, shortened during the peak systemic hypotensive phase of *amyl nitrite* action (Figs. 4*A* and 7). At this phase it lost its crescendo and seemed confined entirely to the first quarter of systole, having a rapid decrescendo after the first sound, which had been intensified by the tachycardia. Occasionally, although very soft, the murmur was more clearly pansystolic at this phase. In one patient the murmur disappeared completely. During the gradual rise in systemic pressure and deceleration of the heart rate the murmur gradually recovered, and usually after 60 seconds had again developed a crescendo in early systole and a rapid diminuendo thereafter. The changes correlated extremely well with the fall and rise of left-to-right ventricular peak systolic pressure gradient (Fig. 4*A*). In 5 patients, amyl nitrite was shown to diminish the minute left-to-right shunt (Fig. 4*B*); the diminution in percentage shunt volume was less striking than the change in intensity of the murmur and in pressure gradient.

In all 8 patients who were given *phenylephrine* the murmur intensified greatly and lengthened considerably, becoming pansystolic. However, the shape of the murmur remained crescendo-decrescendo (Figs. 1, 5, and 8), except during premature systoles and after short preceding diastoles in sinus arrhythmia (Fig. 5). The intensification of the murmur was shown to correlate well with the increased ventricular pressure gradient (Figs. 1 and 5). Since phenylephrine elevated the systemic pressure greatly and the pulmonary arterial pressure only slightly, the gradient across the defect was always considerably elevated.[15] The fall in cardiac output[15] had no influence on intensification of the murmur.

Apparent spontaneous cure of small ventricular septal defect

Two patients, aged 4 and 8 years, who had loud short crescendo-decrescendo systolic murmurs which became much softer after amyl nitrite, were of extreme interest, in that their murmurs spontaneously disappeared during follow-up (Fig. 6). Although the diagnosis of ventricular septal defect was not proved, the site of the murmur, its shape, quality, and behavior with amyl nitrite was sufficient to create strong suspicion of a very small ventricular septal defect. Moreover, in the light of facts now gained from the proved cases the defects must have been very small, possibly in the muscular septum and therefore capable of spontaneous closure during physiologic growth of the heart and septum.

Differential diagnosis

The differential diagnosis is that of a short crescendo-decrescendo systolic murmur unaccompanied by abnormal, clinical electrocardiographic, or radiologic signs. Clearly, the short ejection systolic murmur of large ventricular septal defect with equal

ventricular pressures and elevated pulmonary resistance does not enter the discussion because of the grossly abnormal associated findings.

The murmur under consideration may suggest mild pulmonary or infundibular stenosis, mild aortic or subaortic stenosis, innocent parasternal murmurs of childhood, and pulmonary ejection murmurs due to increased flow or unknown factors. To this list should now be added a minute ventricular septal defect. Whereas a small defect of the Roger type with its classic loud pansystolic murmur is one of the easiest to diagnose, it is now apparent that a small defect cannot be excluded when a murmur is not pansystolic. Once this possibility is suspected, the use of amyl nitrite and/or phenylephrine should quickly confirm or disprove the diagnosis at the bedside (Figs. 7 and 8). Phonocardiography is not essential but may show some finer points of differentiation from ejection systolic murmurs.

Differentiation from mitral incompetence is usually easily made by the site and radiation of the murmur, although the murmurs respond similarly to amyl nitrite and phenylephrine. However, the distinction may not always be easy, as shown in one of our patients (Case 6, L.T., Fig. 8). The short systolic murmur in this girl was loudest at the mitral area, accompanied by a loud third heart sound and a slightly overactive left ventricle. Mitral incompetence seemed much more likely, but the history of a murmur from infancy, the crescendo-decrescendo shape of the high-frequency murmur, and absence of a history of rheumatic fever or features of corrected transposition led us to suspect a minute septal defect; this was confirmed. The possibility, therefore, of a low minute septal defect must be considered when an apical systolic murmur exhibits an early crescendo-decrescendo pattern. Such a shape must be unusual for mild mitral incompetence, in which condition the murmur is either decrescendo, plateau, or has a late systolic crescendo.[1]

Tricuspid valvular incompetence would seldom require consideration. Intensification of the murmur after inspiration and amyl nitrite[2] is an additional distinctive feature.

Discussion

The mechanism of the short crescendo-decrescendo murmur of these minute septal defects is intriguing. In shape and duration this murmur is entirely different from the classic pansystolic murmur of small ventricular septal defect, which murmur extends from the first sound to beyond the aortic second sound, having either a rectangular shape denoting constant intensity or a late systolic crescendo. Yet both murmurs behave similarly after amyl nitrite and phenylephrine, thus proving that both are dependent on the pressure gradient between the left and right ventricles. Why then the difference in configuration? The murmur of a small septal defect is typically pansystolic, because shunt flow is maintained throughout systole by the large pressure differential between the two ventricles, continuing from the isometric contraction phase into the isometric relaxation phase. The plateau or rectangular configuration also implies that the defect remains patent throughout systole, although we suspect that partial occlusion of the defect during late systole may account for the striking late crescendo often encountered in small septal defects. A logical deduction is that the atypical short crescendo-decrescendo murmur is due to occlusion or narrowing of the small defect during early systole. The murmur commences in the usual fashion with the first sound, but instead of maintaining a plateau shape it intensifies very rapidly, suggesting increasing velocity of jet flow. The peak of the crescendo is reached by the first third of systole, which probably reflects the moment of critical narrowing of the orifice, beyond which the available pressure gradient is insufficient to maintain jet flow and velocity. Thereafter, the defect is presumably progressively diminished in size, accounting for the rapid decrescendo of the murmur and its frequent cessation before the aortic second sound.

We have further indirect evidence to support the view that complete or nearly complete closure of the small septal defect during systole accounts for the atypical murmur.

1. When the left-to-right ventricular pressure gradient is greatly increased by phenylephrine, the murmur intensifies and

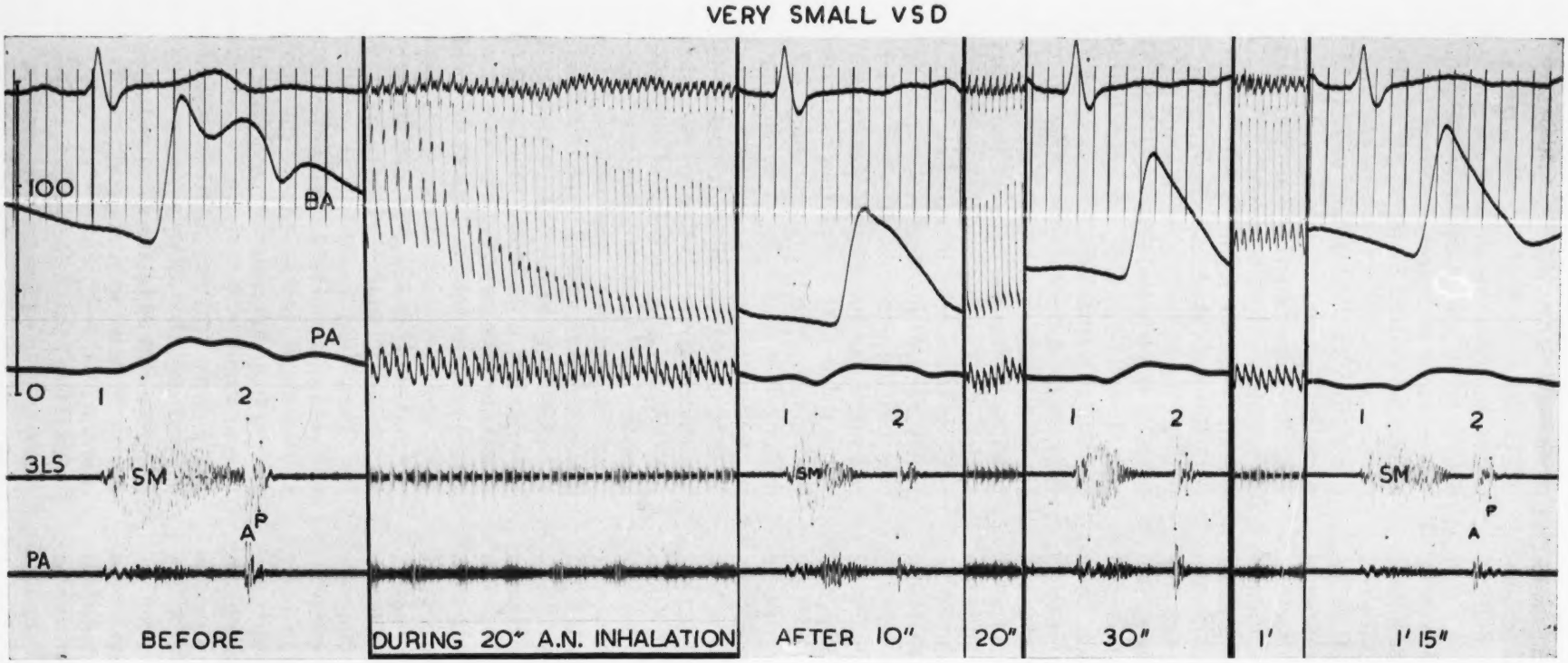

Fig. *4A*. Case 1, T.A. Brachial and pulmonary arterial pressure tracings, synchronously recorded with sound-tracings. Note the wide-peak systolic pressure gradient and the short crescendo-decrescendo systolic murmur. During the 20 seconds of inhalation of amyl nitrite the systemic pressure falls steeply and the pulse contour changes strikingly, whereas the pulmonary pressure falls insignificantly. The resultant gross reduction in ventricular pressure differential causes great shortening and a softening of the systolic murmur. By 1 minute and 15 seconds the gradient and murmur have almost recovered. The response is that of left-sided regurgitant systolic murmur.

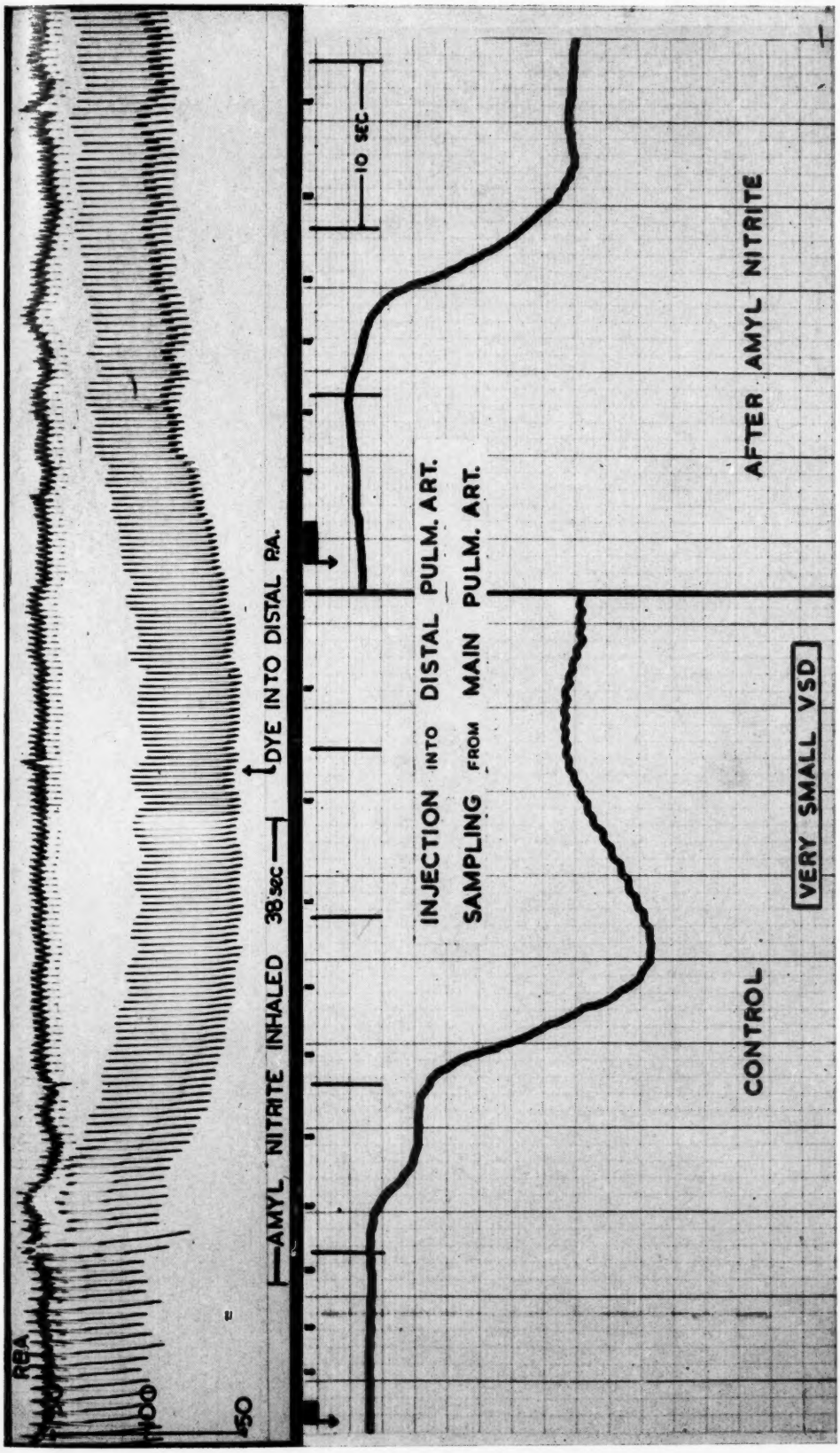

Fig. *4B*. Case 1, T.A. Before amyl nitrite there is a very small left-to-right shunt of about 7 per cent when the systemic pressure is 150/100 mm. Hg. The dilution curve during the peak response to amyl nitrite (blood pressure of 100/50 mm. Hg) (*arrow*) shows a reduction in the left-to-right shunt, accounting for the reduction in murmur after amyl nitrite.

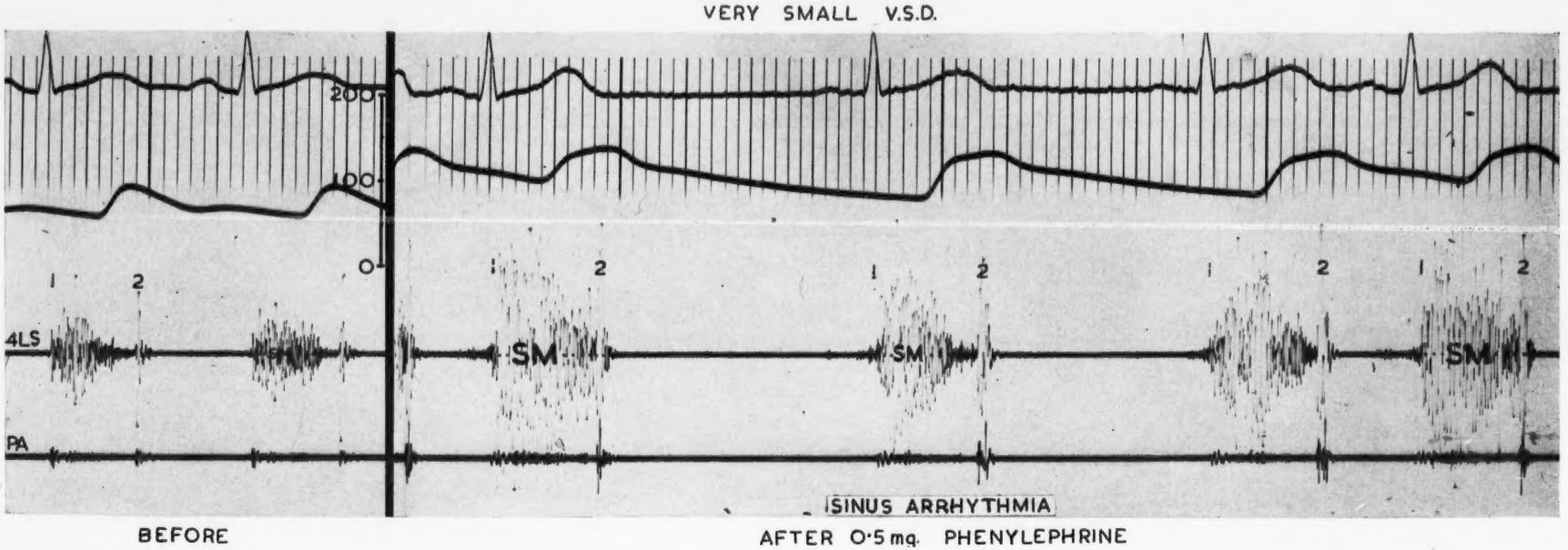

Fig. 5. Case 8, C.M. This figure illustrates two features. The great intensification of the murmur after phenylephrine proves that the murmur which has the appearance of an ejection murmur is a left-sided regurgitant murmur. Marked sinus arrhythmia develops, during which there is little change in systemic pressure but striking and paradoxical change in the length of the murmur and in its intensity in the last quarter of systole. After the short diastole the murmur is longer and louder in end-systole, whereas after the long diastole the murmur has a quicker decrescendo, ending before the second sound (see text).

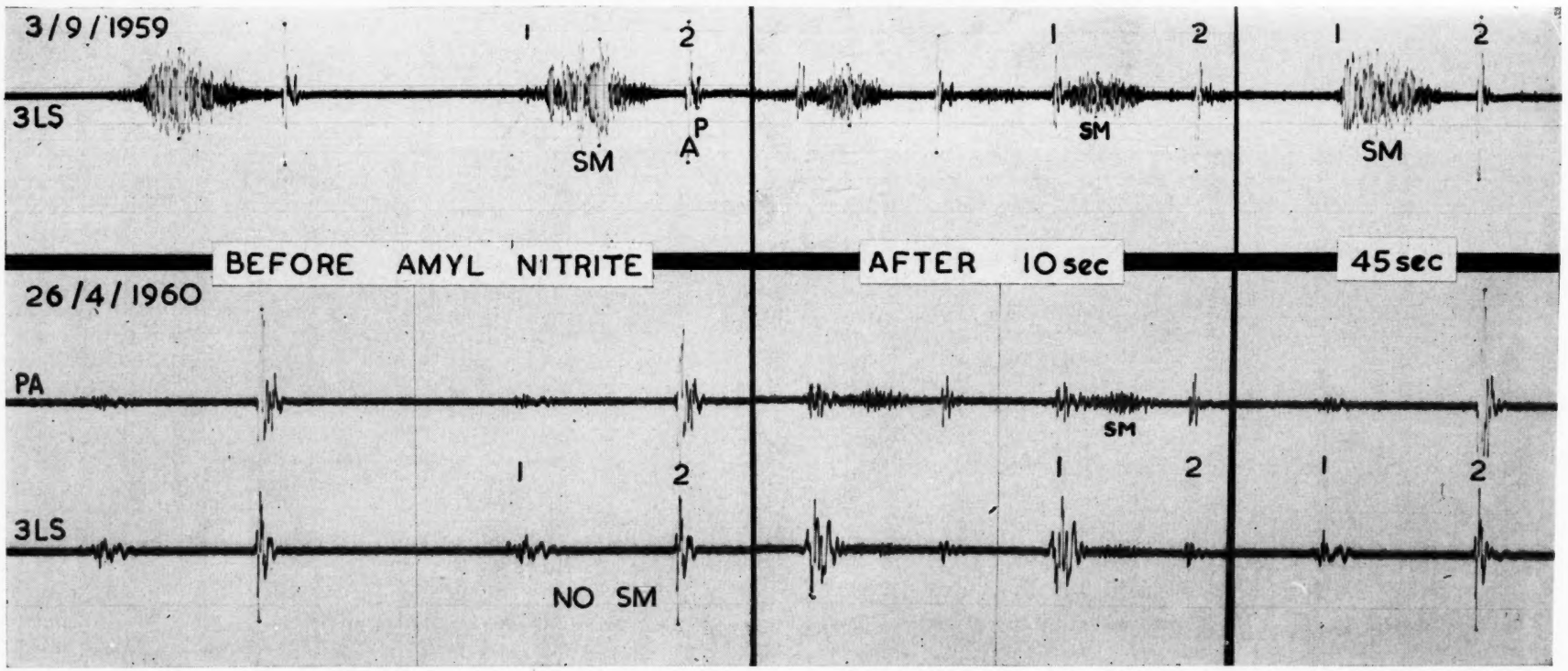

Fig. *6*. Case 11, M.L. Possible spontaneous cure of ventricular septal defect. On Sept. 3, 1959, a localized early systolic, diamond-shaped murmur was recorded at the third left intercostal space (*3LS*). After amyl nitrite the murmur softened considerably, suggesting an atypical, very small ventricular septal defect. On April 26, 1960, the murmur had completely disappeared; no murmur was recordable. After amyl nitrite a soft physiologic ejection murmur emerged at the pulmonary area. The disappearance of the murmur suggested spontaneous cure of a small ventricular septal defect.

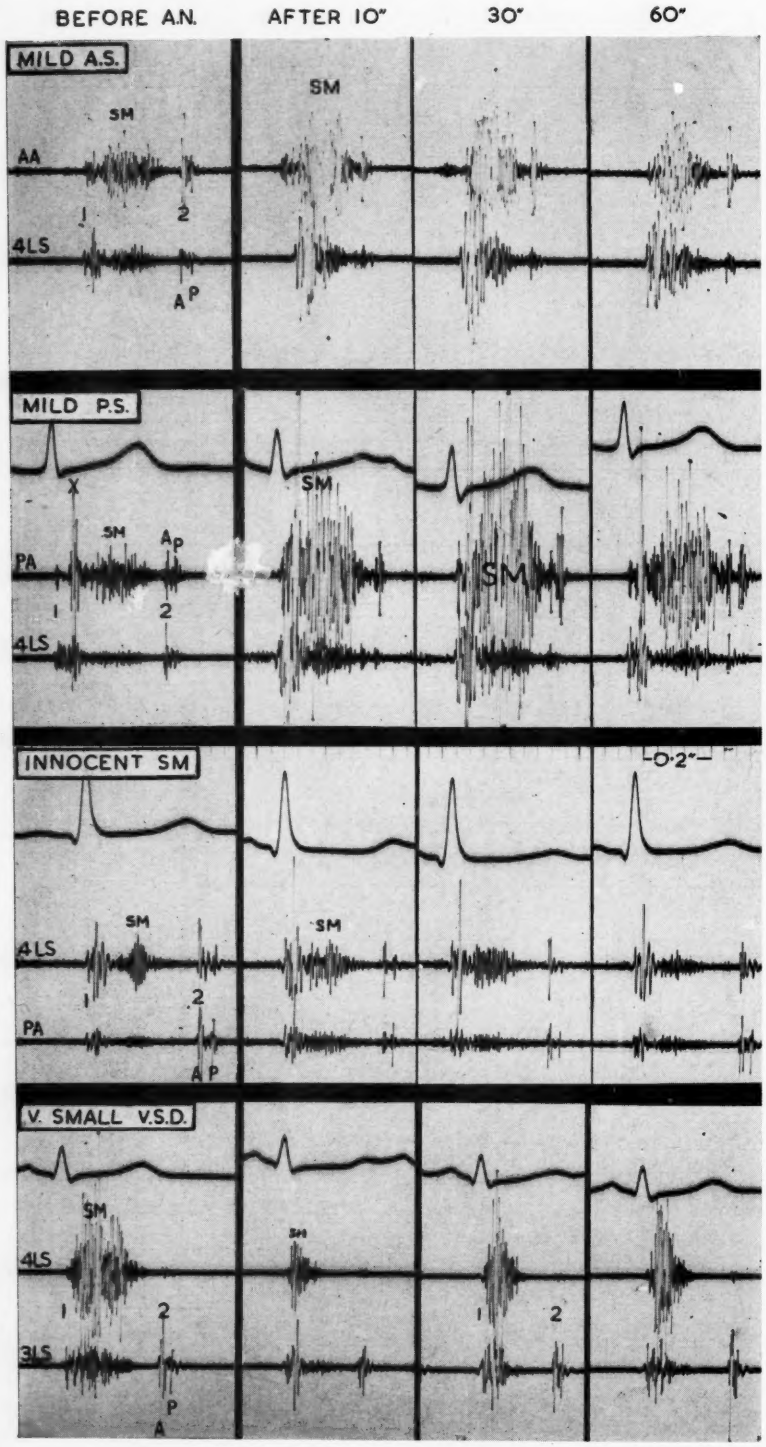

Fig. 7. The value of amyl nitrite in the differentiation of various ejection systolic murmurs, associated with normal electrocardiographic and radiologic findings, from the atypical murmur of very small ventricular septal defect (Case 4, L.D.). All ejection murmurs intensify, especially those due to mild aortic and pulmonary stenosis. The innocent musical parasternal murmur intensifies slightly, suggesting a nonstenotic ejection mechanism. By contrast, the diamond-shaped murmur of minute ventricular septal defect softens and shortens strikingly during the peak response to amyl nitrite, and even at 60 seconds the systolic murmur (*SM*) has not recovered.

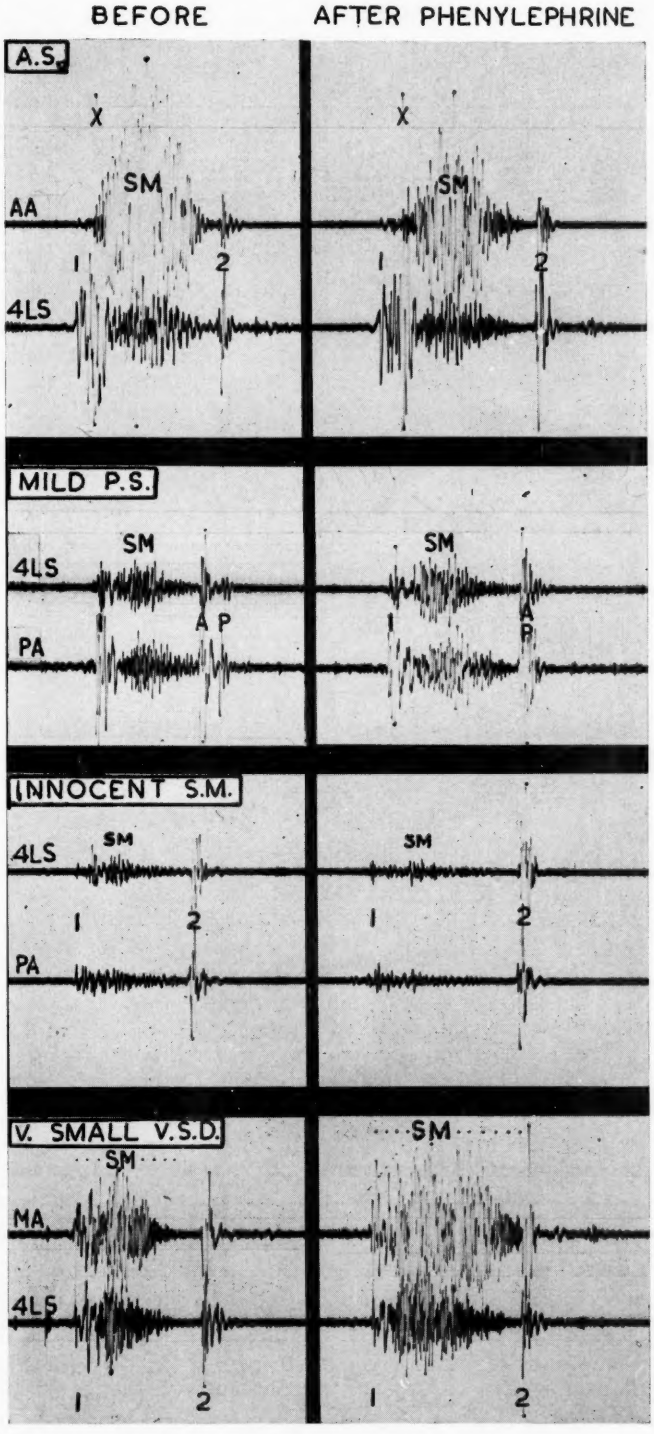

Fig. *8*. Value of phenylephrine in the differentiation of ejection systolic murmurs, with normal ECG and radiologic findings, from murmur of minute ventricular septal defect (Case 6, L.T.). Before phenylephrine there is a close resemblance in shape and duration between all the murmurs, but afterward the ejection murmurs change insignificantly, whereas the diamond-shaped ventricular septal defect murmur intensifies and lengthens greatly, thereby proving a left-sided regurgitant murmur. Although the murmur was maximal at the mitral area, this patient was thought to have a low minute ventricular septal defect in the muscular septum (see text). Note preservation of diamond shape despite pronounced response to phenylephrine, during which the systemic blood pressure rose from 110/50 to 160/90, and pulmonary arterial pressure, from 25/8 to 34/18 mm. Hg.

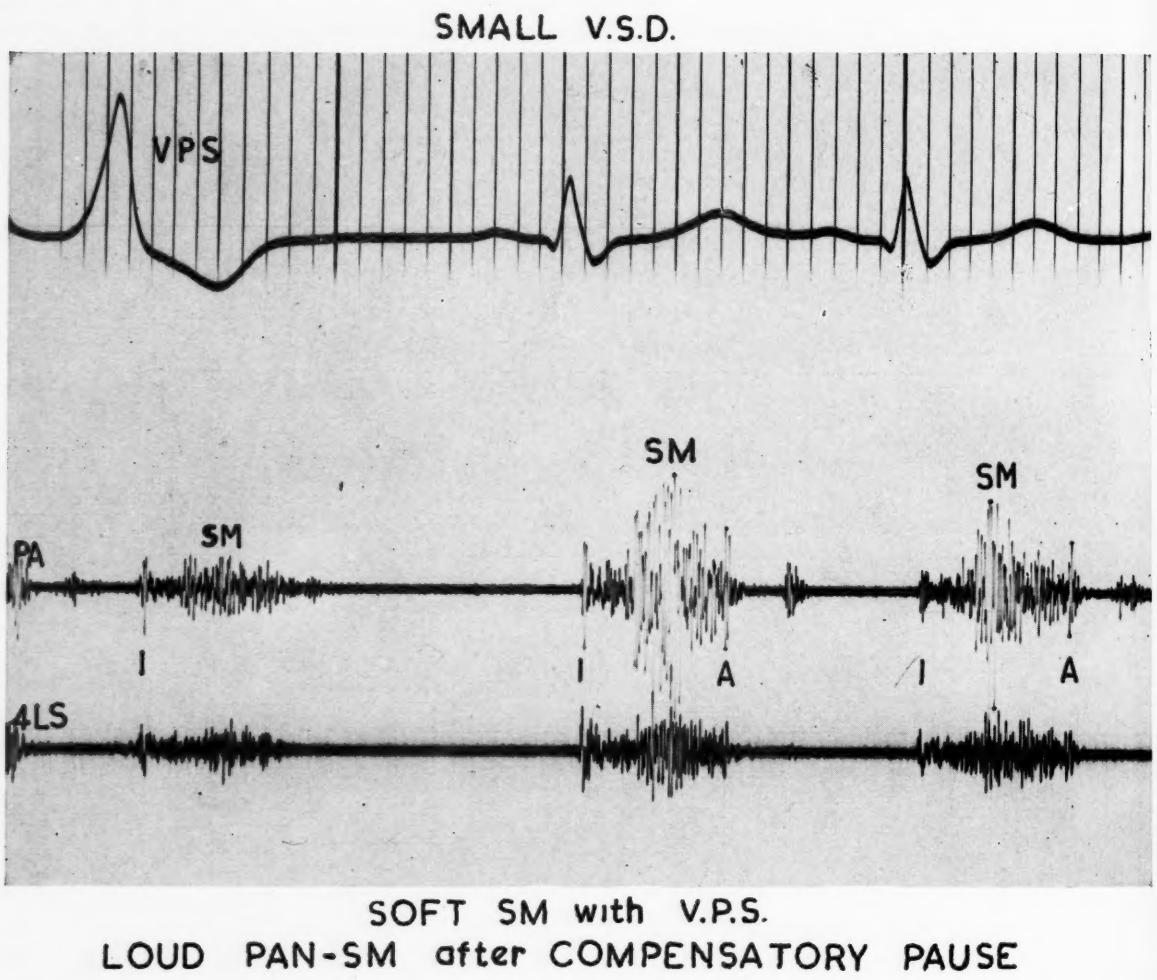

Fig. 9. The usual response of the murmur to arrhythmia in small ventricular septal defect with classic pansystolic murmur. The murmur remains pansystolic throughout, with no significant change in shape, but is softer with the premature systole and slightly louder after the compensatory pause (compare with Fig. 10).

lengthens, reaching the aortic second sound; this proves that the defect is, in fact, patent throughout systole. However, despite these pronounced changes the crescendo-decrescendo shape is maintained, suggesting that the defect does shut down considerably (Figs. 1, 5, and 8). This behavior is quite unlike that of a small ventricular septal defect with a pansystolic murmur, in which situation the entire murmur, and especially the latter half, blows up after phenylephrine.[7]

2. The behavior of the systolic murmur during various arrhythmias is paradoxical. During premature systoles, provided they are not extremely premature, and after the compensatory pause, the classic pansystolic murmur of a small ventricular septal defect remains pansystolic, despite being softer with the premature systole and louder after the pause (personal observations) (Fig. 9). However, in 3 patients with the atypical murmur a paradoxical response resulted from the arrhythmia. The most striking example is shown in Fig. 10. During the premature systole the murmur lost its crescendo and lengthened, becoming a typical plateau or rectangular systolic murmur. However, after the compensatory pause the murmur reverted to its former shape, being then even shorter than before. Even though very loud, the crescendo and abrupt decrescendo occurred in very early systole, suggesting premature and more complete occlusion of the defect. The same paradoxical behavior was observed in 2 patients with sinus arrhythmia (Fig. 5), suggesting that the alteration in

the shape of the murmur is not dependent on ectopic beats, but rather on the changing heart rate. A possible explanation for these observations is that after the short diastole, which resulted in less initial diastolic stretch and consequent less vigorous ventricular (and septal) contraction, the small defect remained patent throughout systole, thus accounting for the pansystolic murmur. However, after the lengthened diastole of the compensatory pause, ventricular contraction would be more vigorous and possibly result in premature and more complete occlusion of the defect, reflected by the very short murmur. In another patient, whose minute defect was thought to be low in the muscular septum, nodal rhythm with ventricular aberration developed for three systoles during the peak response to phenylephrine. Despite the great intensification and lengthening of murmur induced by phenylephrine, the murmur almost disappeared during the three systoles with aberrant ventricular conduction. When ventricular conduction returned to normal, the murmur immediately recovered intensity. Since the heart rate and systemic pressure remained virtually unchanged, the dramatic softening of the murmur was attributed to early systolic closure of the defect by an altered mode of spread of septal contraction caused by the aberrant ventricular activation.

3. During the height of the tachycardia produced by amyl nitrite, when the murmur was maximally softened, it was paradoxically lengthened in 4 patients, with vibrations reaching the aortic second sound. However, during deceleration the murmur shortened whereas the intensity in very

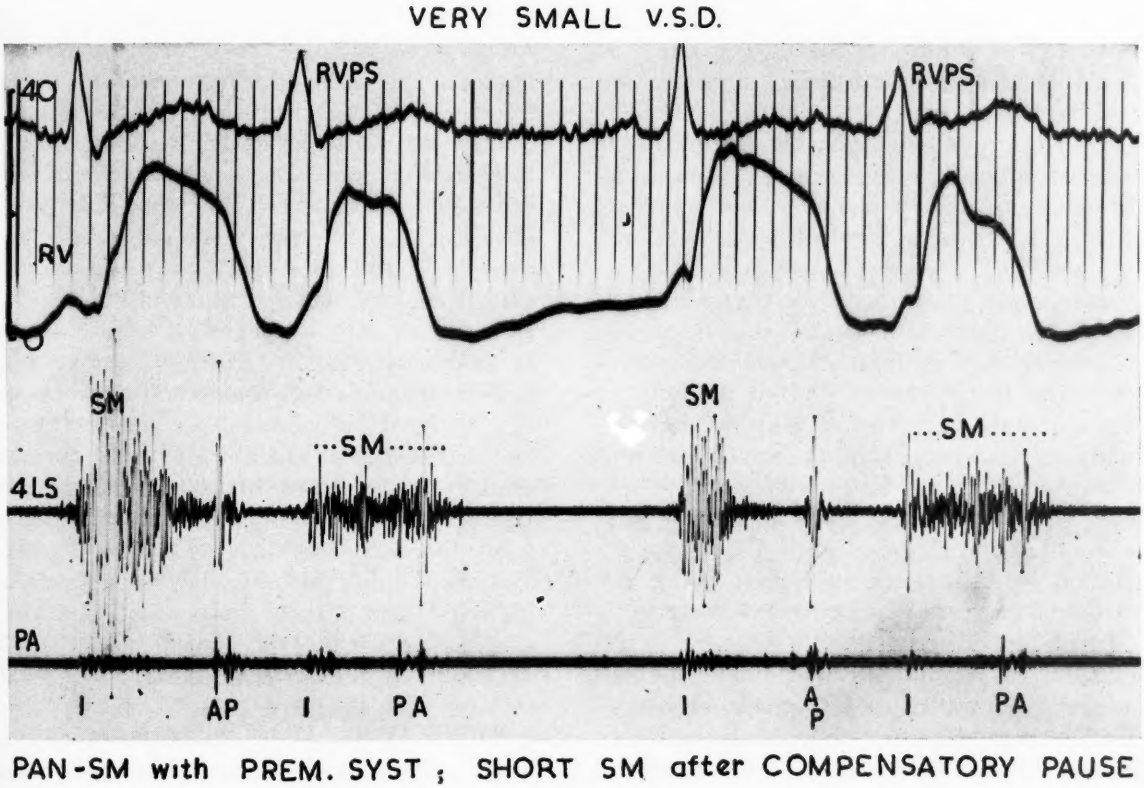

Fig. *10.* Case 8, C.M. Paradoxical response of murmur to arrhythmia in minute ventricular septal defect. The murmur in the first systole is diamond shaped, with a striking crescendo and decrescendo of high-frequency vibrations. With the right ventricular premature systole the murmur becomes a plateau pansystolic murmur, with no mid-systolic crescendo and vibrations of lower frequency. Right ventricular pressure is only slightly reduced and there is reversed splitting of the second sound, with the murmur continuing beyond A_2. After the compensatory pause the right ventricular pressure rises only slightly but the murmur changes strikingly, resuming its former shape and very high frequency; however, the crescendo is even earlier and the decrescendo much more abbreviated. The murmur again becomes plateau pansystolic with the next premature systole (see text).

early systole returned. The crescendo-decrescendo shape was usually restored on return of the heart rate to the normal level, usually after 1 minute. These observations suggest that during the phase of pronounced tachycardia the defect was less effectively occluded in mid-systole, permitting pansystolic flow despite the reduced left ventricular pressure.

Although this evidence strongly supports the idea of a fluctuating size of the orifice in the determination of the shape of the murmur, it does not necessarily imply that the defect is in the muscular ventricular septum, tempting though such an assumption may be. Unfortunately, the site of the defect in the septum could not be determined accurately in this study, since cineangiographic apparatus was not available.[16] In only one patient was there strong clinical and phonocatheter evidence of a low defect in the muscular septum. Although it would appear that a defect in the muscular septum is more apt to become smaller during contraction of the ventricular septum than a defect in the membranous septum, there is some evidence that membranous defects, too, may be squeezed closed by contraction of hypertrophied muscle of the septum and crista supraventricularis.[17] Alternatively, the defect may be occluded by the septal leaflet of the tricuspid valve.[17] Even though we believe that the former possibility is unlikely in our patients in view of their normal dynamics, absence of intraventricular pressure gradient, and triviality of shunt, these arguments do not exclude the possibility of a small membranous defect becoming occluded by the tricuspid valve. Even the strongly suggestive evidence of spontaneous cure of 2 of our patients does not prove the existence of a muscular septal defect. Cineangiocardiography, observations at operation, or necropsy may provide the ultimate proof.

The recognition of small and minute ventricular septal defects is important for several reasons. It is well established that the natural history and prognosis of ventricular septal defect depends on the size of the defect.[18-20] The rarity of encountering ventricular septal defect in persons over 40 years of age has been claimed to support the ultimate poor prognosis.[20] However, it is difficult to believe that small defects in persons with normal dynamics shorten life, and we wonder whether the rarity of ventricular septal defect in adults may partly result from the spontaneous closure of small defects, especially those in the muscular septum. In support of this is our experience with 2 patients who lost their murmurs during follow-up. The possibility of spontaneous disappearance of septal defect was discussed by French,[21] Stamm,[22] and Parkes Weber[23] in 1918, and by others[3,5] since. Possibly, some of the so-called innocent parasternal murmurs of childhood which have been reported to disappear[3] may have been small septal defects undergoing spontaneous cure.

The true incidence of small defects in the muscular septum is unknown. Patients seldom die from them. They are readily missed at routine necropsy, and even at ventriculotomy for large membranous septal defect, because they are buried in-between the trabeculae carneae. The fairly frequent finding of muscular septal defects, sometimes multiple, at the time of operation for membranous septal defects[14] suggests that the reported incidence of muscular defects is too low. When the defect is very small and unassociated with abnormal symptoms and signs, the murmur may be considered to be innocent; if septal defect is suspected, catheterization may either not be considered justified or, if performed, fail to reveal a shunt. We suspect that the incidence of such defects is considerably higher than hitherto stated, but that many of the small defects may close spontaneously with the growth of the heart. We hope that more information about the incidence and natural history will be forthcoming now that the diagnosis of small and minute defects is possible.

Summary

1. A study has been made of 12 patients with atypical systolic murmurs that were believed to be characteristic of minute ventricular septal defects. In 7, left-to-right shunts of under 10 per cent were demonstrated at the ventricular level by refined techniques.

2. Unlike the pansystolic murmur of a small ventricular septal defect, the murmur of a minute defect is confined to early

systole and has a crescendo-decrescendo configuration which simulates an ejection systolic murmur.

3. Since there are no accompanying clinical, electrocardiographic, or radiologic abnormalities in these patients, the atypical murmurs are apt to be confused with left-sided or right-sided ejection systolic murmurs, whether innocent or due to mild stenosis. However, the response to amyl nitrite and phenylephrine readily identifies the atypical septal defect murmur as a left-sided regurgitant murmur.

4. Simple auscultation and phonocardiography using amyl nitrite and/or phenylephrine proved superior in diagnosis to conventional methods of cardiac catheterization in the diagnosis of minute septal defects.

5. Routine methods of cardiac catheterization and systemic arterial dye-dilution techniques failed to demonstrate such diminutive shunts. However, the technique which employs two venous catheters for obtaining dye-dilution curves from the right heart and intracardiac phonocardiography successfully established the diagnosis. The methods and use of vasoactive drugs to manipulate the shunt are discussed.

6. The mechanism of the crescendo-decrescendo shape of the murmur is believed to be partial occlusion of the small defect in early systole during contraction of the ventricle and septum. The reasons for this belief are fully discussed.

7. The site of the defect in the ventricular septum could not be established, although in one patient there was good evidence of a defect in the low muscular septum.

8. In 2 patients the murmur disappeared during follow-up, suggesting spontaneous closure of the defect.

9. Now that the diagnosis of very small septal defects with atypical systolic murmurs is possible, more light should be thrown on their incidence and natural history.

Addendum

After this paper had been submitted for publication, an important paper was published by Evans and associates,[24] showing that spontaneous closure is not uncommon in small septal defects and may rarely occur with lesions large enough to present initially with congestive cardiac failure. The authors confirm that a short, early, high-frequency systolic murmur indicates a very small septal defect and have observed loud pansystolic murmurs in infancy becoming shorter and softer before ultimately disappearing. By comparing catheterization data in 5 patients with sound-tracings, they showed that softening and shortening of the murmur was associated with decreasing magnitude of left-to-right shunt. That disappearance of the murmur indicated disappearance of the shunt was established by recatheterization in 2 patients.

The authors also believe that defects giving these characteristics are likely to be located in the muscular septum. In one subject a selective cineangiocardiogram from the left ventricle demonstrated a small defect in the lower interventricular septum, and in 2 additional patients, intracardiac sound-tracings revealed a short early systolic murmur localized to the apical region of the right ventricle, suggesting a muscular septal defect.

We wish to thank members of the staff of Groote Schuur Hospital for referring cases for investigation, and the Superintendent, Dr. J. Burger, for his permission to publish. We gratefully acknowledge the great assistance received from our chief technician, Mr. L. W. Piller, and that of Mr. R. deMeneau, Miss S. Joseph, and Miss A. Strauss, as well as the assistance of the nursing staff. We wish to thank Mrs. C. M. Hall for clerical assistance.

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Case reports

Corrected transposition of the great vessels
Report of 2 cases

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In corrected transposition of the great vessels the aorta is situated anteriorly and usually to the left, and the pulmonary artery, posteriorly and usually to the right. The route of blood flow, however, is normal. The correction occurs by inversion in different regions, bulbar, sinoatrial, or ventricular.[2] The venous blood of the systemic veins enters the right atrium and passes through the bicuspid atrioventricular valve to enter a ventricle with the structural appearance of a left ventricle, from which the pulmonary artery takes off. The arterial blood of the pulmonary veins enters the left atrium and passes through a tricuspid atrioventricular valve to enter a ventricle with the structural appearance of a right ventricle, from which the aorta takes off. There is inversion of the coronary arteries.[7]

The malformation is rarely isolated.[2] In most cases there are septal defects or valvular lesions. Incompetence of the atrioventricular valve on the arterial side ("mitral incompetence") has been reported.[4-6] Various grades of atrioventricular block are a common feature.[1,3-6,8] As in many other congenital heart malformations the condition was first recognized at postmortem. When the clinical picture was described, the antemortem diagnosis became possible. The clinical findings vary to a great extent, however, depending on the type of associated lesions.

Within a period of one month, we met with two cases diagnosed clinically.

Case reports

Case 1. The physical and mental development of this 7-year-old boy had been normal. Since infancy, he had suffered from dyspnea on exertion, but had never been cyanotic. A systolic murmur was first detected when he was 4 years old. Examination of the cardiovascular system showed a heart rate of 56 beats per minute. The blood pressure was 130/75 mm. Hg in the upper and lower limbs. There was no precordial bulge. The apex beat was heaving and located in the fifth intercostal space at the mid-clavicular line. There was a palpable second sound over the pulmonary area. Auscultation revealed marked accentuation of the second sound, which was not split and had its maximal intensity over the second left intercostal space. The first sound was changing in intensity. A Grade 4 early systolic murmur was heard over the base, as intense to the right as to the left of the sternum. A longer

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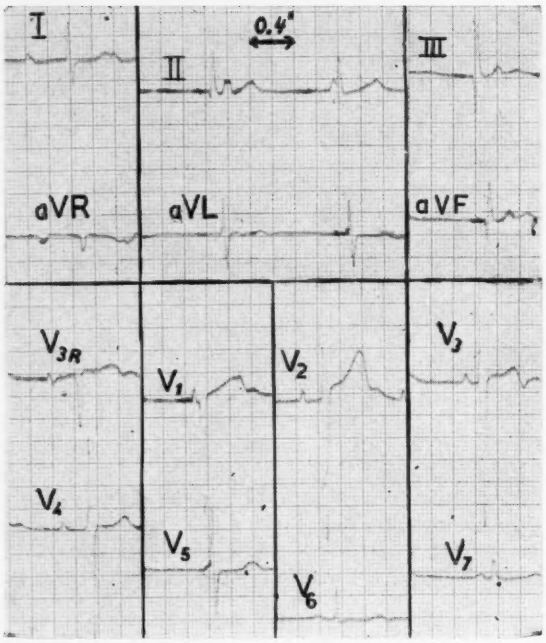

Fig. *1.* ECG in Case 1. Note a complete A-V block, a deep Q in Leads III and aV_F, a deep S in V_1, and slight depression of S-T in V_6.

systolic murmur of the same intensity was audible over the apex and was transmitted to the left axilla and to the back. There was also a short low-frequency mid-diastolic murmur.

The ECG (Fig. 1) showed a complete A-V block, a deep Q in Leads III and aV_F, a deep S in Lead V_1, and slight depression of S-T in Lead V_6.

ROENTGENOLOGIC EXAMINATION. The roentgenogram (Fig. 2) showed a markedly enlarged heart, with an upturned apex and an abnormally straight line in the upper left border. The aortic arch had a normal position to the left. In the lateral view the heart had an increased surface of contact with the anterior chest wall, and the left atrium was slightly dilated. The central lung vessels were somewhat widened.

HEART CATHETERIZATION. Catheterization data are given in Table I. The catheter, introduced into a left cubital vein, passed from the venous ventricle out into the pulmonary artery in a more medial and posterior position than normally (Fig. 3). There were no left-to-right shunts. The systolic pressure in the pulmonary artery was increased, with a large pulse amplitude and only a slight increase in the mean pressure. A systolic pressure gradient of 19 mm. Hg was found across the pulmonary valve. In the presence of complete A-V block, the expected increase in the stroke volume can explain this pressure gradient without any anatomic stenosis. The pulmonary arterial wedged pressure was not increased, but the v waves were abnormally high and showed a rapid fall (Fig. 4).

Case 2. The physical and mental development of this 5½-year-old girl had been normal. She had had no heart symptoms, but was admitted to the hospital because of enlarged breasts, a condition which had its onset 8 months prior to hospitalization. At routine examination a murmur was discovered. Physical examination revealed true glandular hypertrophy of the breasts. The heart rate during sleep was 97 beats per minute. The blood pressure was 105/65 in the upper limbs and 120/65 mm. Hg in the lower limbs. There was no precordial bulge. The apex beat was normal. The second sound was palpable over the pulmonary area. On auscultation there was marked accentuation of the second sound, which was not split and had its maximal intensity in the second left intercostal space. There was a Grade 4 systolic murmur, of rather high frequency, which ended before the second sound, and which was of maximal intensity over the middle of the sternum at the level of the third intercostal space. On phonocardiography the murmur was found to be diamond shaped.

The ECG (Fig. 5) showed a normal sinus rhythm, with a slightly prolonged P-Q time (0.20 second) and a deep Q in Leads III and aV_F.

ROENTGENOLOGIC EXAMINATION. The roentgenogram (Fig. 6) showed a rather normal-sized heart,

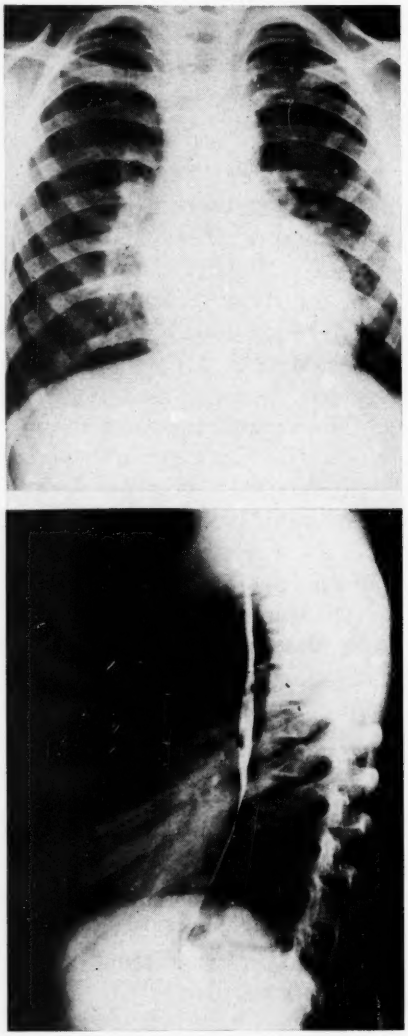

Fig. *2.* Case 1. Enlargement of the heart, upturned apex, abnormally straight upper left border, and slightly dilated left atrium.

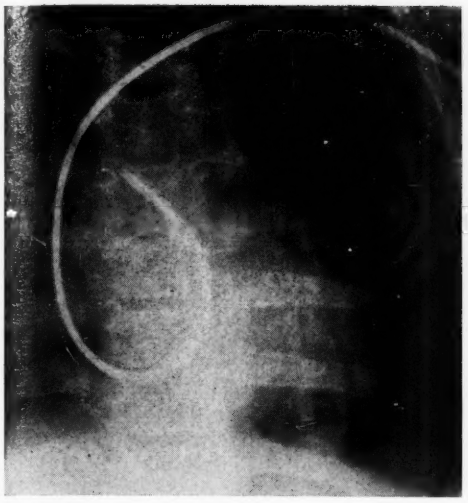

Fig. *3.* Case 1. The catheter, introduced from the left arm, passes through the right atrium and venous ventricle into the pulmonary artery, which has a medial position.

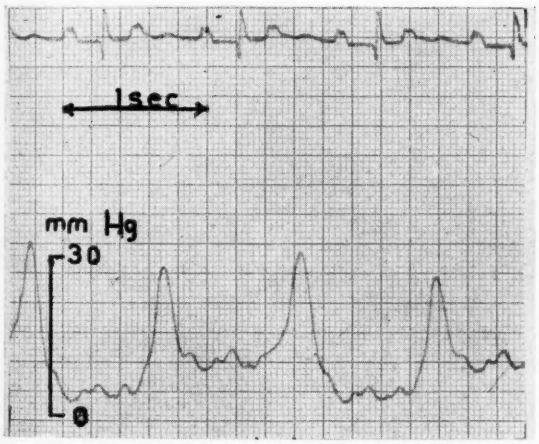

Fig. *4.* Case 1. Pulmonary arterial wedged pressure. Note the high v waves.

but one that was abnormal in configuration. The apex was upturned and the left upper border was abnormally straight. The great vessels were not seen at their usual site on the left of the mediastinum. There was a right aortic arch, and the descending aorta passed to the right. In the lateral view the heart showed an increased surface of contact against the anterior chest wall. The left atrium was not enlarged. The vascularity of the lungs was normal.

HEART CATHETERIZATION. Catheterization was performed from the saphenous vein. When the catheter passed from the venous ventricle out into the pulmonary artery, its position was more medial and posterior than occurs normally (Fig. 7). There was a pressure gradient across the pulmonary valve of 23 mm. Hg. No left-to-right shunt was present. The pulmonary wedged and the pulmonary arterial pressures were normal (see Table I).

ANGIOCARDIOGRAPHY. No film changer was available. Twenty milliliters of 70 per cent Urographine was injected by hand through the catheter placed in the venous ventricle, and a few exposures were made within 8 seconds. The pulmonary artery was found to be placed to the right of the ascending aorta (Fig. 8).

Discussion

In both of these cases a presumptive diagnosis was made with the aid of physical findings, ECG and roentgenologic examination. The diagnosis was confirmed by heart catheterization. A markedly accentuated single second sound over the pulmonary area, in conjunction with an electrocardiogram and roentgenologic picture which excluded pulmonary hypertension of a high degree, was a characteristic feature. The roentgenologic examination gave also some positive evidence of transposition of the great vessels, by absence of the pulmonary artery shadow at its normal site. The transposition must have been corrected, because no cyanosis was present. The heart catheterization was decisive for the diagnosis, since the position of the pulmonary artery was established by passage of the catheter from the venous ventricle into the pulmonary artery. Furthermore, the results of heart catheterization were important for the diagnosis of the associated lesions.

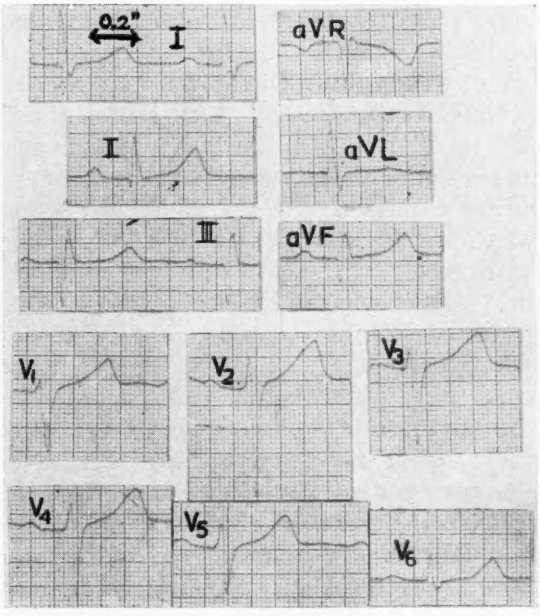

Fig. *5.* ECG in Case 2. Note slightly prolonged P-Q time and deep Q in Leads III and aV_F.

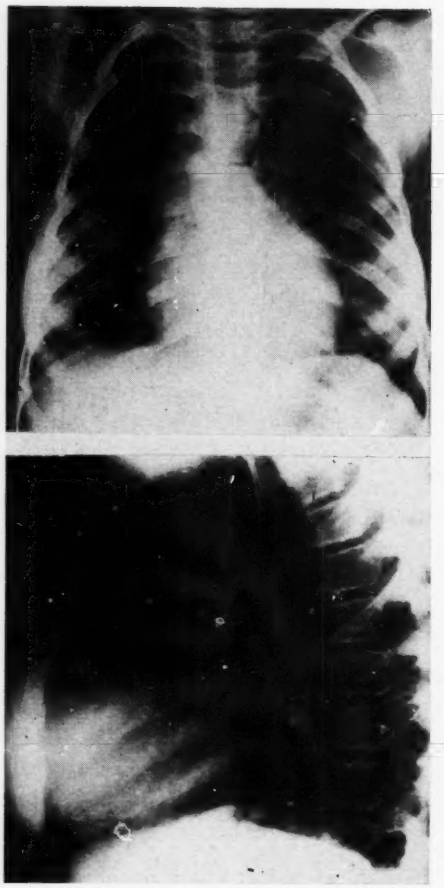

Fig. *6*. Case 2. Note the upturned apex, straight left upper border of the heart, and right aortic arch.

Because of the altered position of the great vessels and the ventricles the physical findings caused by the associated lesions are often atypical. The systolic murmur of pulmonary stenosis or atrial septal defect will have an altered position and intensity as a result of displacement of the pulmonary orifice posteriorly, to the right and somewhat caudally. In Case 1 it was not possible to ascertain by means of physical examination alone what associated lesions were present. Since there was complete atrioventricular block, the systolic murmur could have been due, at least partially, to the large stroke volume. The intensity of the murmur, however, was as marked over the apex and in the left axilla as over the roots of the great vessels. Furthermore, the mid-diastolic low-frequency apical murmur was so intense that it would indicate an increased diastolic filling of the ventricle (left or right) larger than that in a case of atrioventricular block. The x-ray film

Fig. *7*. Case 2. The catheter, introduced from the right saphenous vein, passes through the right atrium and venous ventricle into the pulmonary artery, which has a medial position.

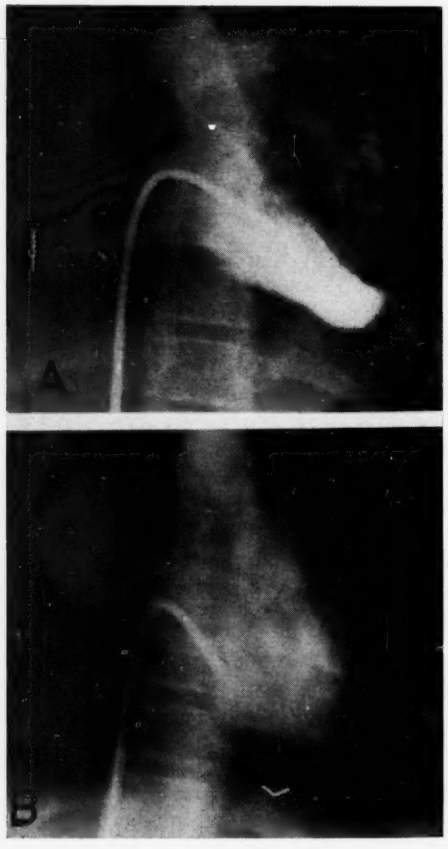

Fig. *8*. Case 2. Angiocardiography with injection of contrast medium into the venous ventricle. In *A* the venous ventricle and the pulmonary artery are filled, and in *B* the arterial ventricle and the aorta are filled. The ascending aorta is situated to the left of the trunk of the pulmonary artery.

Table I. *Results of heart catheterization*

	Oxygen content (volume per cent)				*Pressures (mm. Hg)*			
	S.V.C.	*Right atrium*	*Venous ventricle*	*Pulmonary artery*	*Right atrium*	*Venous ventricle*	*Pulmonary artery*	*P.C.V.*
Case 1	11.5	11.3	11.2	11.3	4	68	49/9	Mean 10 v wave 27
Case 2	13.1	——	13.4	13.4	2	50/2	27/7	Mean 10

Gas analysis by the Van Slyke method. Pressures recorded by electromanometer (Elema).

showed a slightly enlarged left atrium, probably more enlarged than the other chambers, and the lung vessels were somewhat dilated. Therefore, incompetence of the atrioventricular valve on the arterial side or an atrial septal defect was suspected. By heart catheterization it was established that no atrial septal defect was present, and the shape of the pulmonary arterial wedged pressure curve indicated an incompetence of the atrioventricular valve.

In Case 2 the systolic murmur was short, early systolic, and diamond shaped. It could be explained by a mild pulmonary stenosis or a large atrial septal defect. The roentgenologic examination, however, did not indicate an atrial septal defect. The localization of the murmur was more medial than the normal pulmonary area and corresponded to the position of the pulmonary orifice in corrected transposition. At heart catheterization, pulmonary stenosis of a mild degree was found.

Gasul and associates[4] found the second sound to be split over the second right intercostal space but single and loud to the left of the sternum in a case of corrected transposition of the great vessels associated with a probable "mitral insufficiency." In our cases it was not possible to hear or record the pulmonary component of the second sound, which can be explained by the dorsal position of the pulmonary orifice and a very low diastolic pressure in the pulmonary artery.

In many of the rather few cases with a report of the clinical findings there was an atrioventricular block. In one of our two cases there was a complete, and in the other a Grade I, atrioventricular block. Otherwise, variations in the ECG depend on the position of the ventricles and the associated malformations giving rise to ventricular hypertrophy or dilatation. We did not find a reversal of the QRS pattern as has been described in some cases.[1] In both of our cases there was a deep Q in Leads III and aV_F, which has also been a finding in most cases reported earlier.[1,3,4,6] This pattern may be an important feature.

The recognition of corrected transposition has a practical importance in cases in which intracardiac operation is contemplated, because the abnormal position of the coronary arteries can interfere with a proper incision through the ventricular wall. Therefore, the anatomy of the coronary arteries should be outlined by the aid of angiocardiography before operation.

Summary

Two cases of corrected transposition of the great vessels have been reported: one with an associated "mitral incompetence" and a complete atrioventricular block, and one with mild pulmonary stenosis and Grade I atrioventricular block. In both cases, proper evaluation of the physical findings, ECG, and roentgenologic appearance enabled us to reach the diagnosis which was confirmed by heart catheterization.

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Longevity in tetralogy and trilogy of Fallot
Discussion of cases in patients surviving 40 years and presentation of two further cases

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With the successful development of surgical techniques for the relief or correction of congenital heart lesions, interest in the natural history of these defects was heightened. The advances in cardiac surgery have followed so closely on the development of accurate investigatory techniques that the clinical course of many congenital heart defects seems likely to remain imperfectly understood. Rosenthal[29] has suggested that clinical material accumulating from geriatric units might reveal a greater number of older patients with congenital cardiac malformations than was formerly appreciated.

In this paper, the cases of two patients with cyanotic congenital heart disease are presented; both of the patients died in a geriatric unit. One patient with the tetralogy of Fallot appears to be the oldest woman (69 years) whose case has been recorded so far. The other case is that of a woman with the trilogy of Fallot who lived to the age of 71 years.

Trilogy of Fallot

Pulmonary stenosis with intact ventricular septum was at first thought to be a rare congenital heart defect. In Abbott's[1] 1936 series of 1,000 cases of congenital heart disease, only 9 of the patients presented this lesion. Subsequent investigators, however, have found this early impression to be misleading. Wood,[2] in 1950, found 24 cases of pulmonary stenosis with intact ventricular septum in 200 cases of congenital heart disease, an incidence of 12 per cent. Geraci and associates[3] reported 6 cases of congenital pulmonary stenosis among 300 necropsy specimens at the Mayo Clinic, and Campbell[4] found the frequency of pulmonary stenosis in 1,130 cases of congenital heart disease to be 10 per cent, or 113 cases. Abrahams and Wood[5] found 71 cases of pulmonary stenosis in 689 cases of congenital heart disease, an incidence of 11.6 per cent.

However, the association of pulmonary stenosis with intact ventricular septum but with interatrial communication is less common. Among the 24 cases of Wood[2] mentioned above, there were atrial septal defects in 5, an incidence of 2.5 per cent. Campbell[4] noted that of his 113 cases with pulmonary stenosis, 41 were cyanotic, that is, 6 per cent of the total series. Of Abrahams and Wood's[5] 71 cases of pulmonary stenosis, there were atrial septal defects in 15, including 8 cases in which there were reversed interatrial shunts.

Following Fallot's[6] description of 7 cases of pulmonary stenosis with intact ventricular septum and interatrial communication, this lesion has been known as the "trilogy of Fallot."

The age to which patients with the trilogy of Fallot may survive has been mentioned

Received for publication Dec. 9, 1960.

in several surveys. In 1949, Selzer and associates[7] reviewed the reports of 29 autopsied cases of the trilogy and found the average age of the patients to be 20 years. Soulié and associates[30] quote Épinat, who, in 1950, found 11 cases in which death occurred between 20 and 30 years, 3 between 30 and 40 years, and 5 between 50 and 60 years. They also quote Guyot, who, in 1945, recorded 7 cases in which death occurred between 20 and 30, 1 between 30 and 40, and 3 between 50 and 60 years. They themselves in their series found 10 cases in which death occurred between 20 and 30 years, 5 between 30 and 40 years, and 1 in which death occurred at 44 years.

A number of individual reports of longevity with this disorder are on record. White and associates[8] reported the case of one of the oldest patients, a man who died at the age of 75 years. Geraci and associates[3] reported the case of a man who died at 53 years. Vogelpoel and associates[9] included in their series 2 cases of patients who lived to be 42 and 49 years. The cyanosed patients living to the age of 44 and 42 years reported by Torner-Soler and associates[10] and Gadboys and associates,[11] respectively, had pulmonary stenosis with closed ventricular septum. Swan and associates[12] included in their series of 22 patients a man who lived to the age of 50 years.

Long-term survival in cases of trilogy of Fallot would not be unexpected when the pulmonary stenosis was slight to moderate, but the following report of a patient surviving to the age of 71 years is of interest because of the high degree of stenosis.

Case report

The patient, a woman, was first admitted to hospital at the age of 68 years. In childhood she had been breathless with effort and susceptible to respiratory infections, but she was not then cyanosed. She had not been greatly handicapped by dyspnea, and had worked as a waitress, domestic servant, and a machinist. She married when she was 25 years old and became pregnant three times, miscarrying twice and finally being delivered of a full-term live infant. When she was 34 years old, she underwent an operation for correction of retroversion of the uterus, and this procedure was complicated by an episode of "congestion of the lungs." At about middle age she developed increasingly severe attacks of bronchitis, and her effort tolerance progressively declined. Cyanosis was first noted at this time. In her later years, cyanosis deepened, and her range of activity became progressively more limited. At the time of admission to hospital she had been an invalid for some years.

When examined, she was not dyspneic at rest. There was marked central cyanosis but no clubbing. The pulse was regular, and the blood pressure was 200/100 mm. Hg. The jugular venous pulse showed prominent "a" waves. The venous pressure was not elevated, nor was the liver enlarged. There was slight ankle and sacral edema. The lung bases were clear. The apex beat was in the fifth left intercostal space in the anterior axillary line. There was a long systolic murmur of moderate intensity, widely conducted and best heard at the pulmonary area. The second sound was single and faint.

The hemoglobin was 16.9 Gm. per 100 ml. The erythrocyte count was 6,200,000 per cu. mm. The sedimentation rate was 2 mm. in 1 hour. The electrocardiogram (Fig. 1) showed the pattern of incomplete right bundle branch block and atrial flutter, with some degree of right ventricular hypertrophy. The chest roentgenogram revealed slight cardiac enlargement, with a cardiothoracic index of 61 per cent.

During the first 4 weeks of her admission the edema disappeared and cyanosis lessened. She became ambulant again and was discharged.

Nine months later she was again admitted in mild congestive failure, with the same symptoms and with signs of a recovering hemiparesis involving her left leg. During this admission the arterial oxygen saturation was 84 per cent at rest. With digitalis and diuretics the signs of failure resolved and she was again discharged.

Over the next 3 years her course was one of progressively deepening cyanosis and decreasing activity, with one mild episode of congestive failure. When she was admitted for the last time at the age of 71 years, her electrocardiogram showed atrial flutter with an irregular ventricular response. Radiologically, the heart size had increased and the pulmonary artery had become more prominent. She died some days later; during the last days

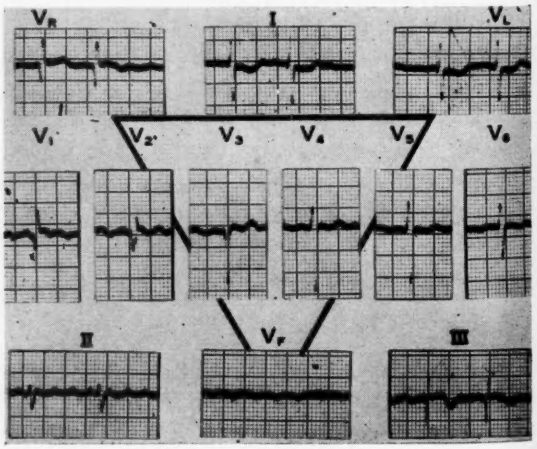

Fig. *1.* Electrocardiogram of patient with the trilogy of Fallot, showing atrial flutter with irregular ventricular response, moderate right ventricular hypertrophy, and incomplete right bundle branch block pattern.

Fig. *2.* Heart of patient with the trilogy of Fallot, showing the right ventricular hypertrophy.

she remained extremely cyanosed and in moderately severe congestive failure.

At postmortem examination, the heart weighed 590 grams (Fig. 2). Both ventricles were markedly hypertrophied; the right ventricular wall was 11 mm. thick and the left ventricular wall was 16 mm. The pulmonary valve showed a dome-shaped fusion of the cusps which reduced the central lumen to a diameter of 5 mm. (Fig. 3). This lumen was further narrowed by firmly attached vegetations, making the effective outflow tract 3 mm. in diameter. The pulmonary artery was dilated beyond the stenosis. There was a small atrial septal defect, 3 mm. in diameter, and the foramen ovale was patent. The heart was otherwise normal; the ductus arteriosus was obliterated. On histologic examination the vegetations on the pulmonary valve were found to be consistent with an old healed bacterial endocarditis.

Discussion

The most important factor governing longevity in patients with trilogy of Fallot would appear to be the severity of the pulmonary stenosis. In our patient there was necropsy evidence of at least moderate constriction of the pulmonary valve; the diameter initially was probably 5 mm. and this was subsequently constricted to 3 mm. by fibrotic vegetations. This aperture may be compared with the 3-mm. opening in White's[8] patient who was 75 years old and the 8-mm. opening in Geraci's[3] patient who was 53 years old. The patients whose cases were quoted by Vogelpoel,[9] by Torner-Soler,[10] and by Gadboys[11] were alive at the time of reporting. The size of the lumen of the valve was not stated in Swan's case.[12]

In our patient, cyanosis did not appear until middle life, but had been present for many years before death. It is possible that it followed the encroachment of vegetations on the lumen of the valve. Although Campbell[4] commented that cyanosis tended to be later in appearance in the older patients, other reports would suggest that the age of onset of cyanosis does not closely relate to the prognosis: in Campbell's older, cyanosed patients (20 to 33 years) the usual time of onset was between 12 and 16 years. Swan and associates,[12] in their series of 22 patients with the trilogy, found that 18 were cyanosed before 12 years, and 4 became cyanosed after 10 years of age. The 44-year-old living patient of Torner-Soler[10] became cyanosed at 38 years of age, and the 42-year-old patient of Vogelpoel[9] be-

Fig. *3.* The pulmonary valve of patient with the trilogy of Fallot, seen from above.

came cyanosed at 40 years. On the other hand, White's[8] 75-year-old man was blue from the time of his early youth; Gadboy's[11] 42-year-old living patient was termed a "blue baby" at birth, and Vogelpoel's[9] 49-year-old patient was cyanosed at 10 years of age. Geraci's[3] 53-year-old patient was never cyanosed.

The interatrial communication in our patient consisted of a septal defect as well as a patent foramen ovale. Selzer and Carnes,[13] in 1953, reviewing cases of pulmonary stenosis, concluded that when an interatrial communication is present it is almost always a patent foramen ovale. Campbell[4] thought that quite frequently the defect was not a foramen ovale, and certainly the presence of both in our case would support him.

Tetralogy of Fallot

The tetralogy of Fallot presents a wide spectrum of clinical pictures, ranging from the deeply cyanosed, severely limited patient to the patient with the so-called "acyanotic" form of this defect. Because of this diversity of presentation, series of unselected cases may not be representative of all variants of this condition, and the figures quoted for average survival may have little significance in the assessment of prognosis in the given individual. Maud Abbott[1] estimated the average length of life to be 6 years if the pulmonary artery showed atresia, and 12 years if it was stenosed. Donzelot and associates,[21] in 1949, reporting cases in 200 living patients found that 13 patients were between the ages of 21 and 30 years, and that 1 patient was 45 years old. Guyot,[19] in 1945, reviewing 81 cases, found that 16 patients died between the ages of 20 and 30 years, 2 died between 30 and 40 years, and 1 was alive over 40 years. Soulié and associates,[30] in 1956, studied 144 patients with this defect, all alive except 4, and found 8 between 20 and 30 years of age, 2 between 30 and 40 years, and 2 over 40 years.

A number of reports of individual cases in which survival was prolonged into adult life are in the literature. In 1871, Bock reported the case of a patient who died at 40 years of age; the oldest patient in the series which Fallot reported in 1888[6] died at 36 years of age, and until White and Sprague,[14] in 1921, described their famous musician who lived to the age of 59 years, no survivor to an older age had been found. Since then, 21 other patients surviving over the age of 40 have been reported.

Case report

A 68-year-old woman was admitted to hospital because of gradually increasing confusion, fainting, and chest pain. She had been told in childhood that she had a "hole in her heart," and, as long as she could remember, she had been cyanosed and dyspneic on exertion. As a child she could walk slowly without discomfort, but dyspnea followed even slight effort, and was best relieved by squatting. Episodes of unconsciousness sometimes accompanied exertion in hot weather, but these became less frequent in adult life. Between the ages of 17 and 21 years, she was said to have improved. She was employed as a teacher from the age of 19 years. When she was 35 years old, she emigrated from England to New Zealand and continued teaching until her retirement in her late fifties. During her later life, effort caused irregular palpitations and the occurrence of sharp attacks of retrosternal pain two or three times daily.

On admission to hospital she was moderately dyspneic at rest and was severely cyanosed. There was only slight clubbing of the fingers. She had a marked thoracic kyphoscoliosis and a prominent precordium. The pulse was irregular, with multiple extrasystoles. The blood pressure was 140/80 mm. Hg. The jugular venous pressure was elevated 5 cm. above the sternal angle, and the liver was palpable two fingerbreadths below the costal margin. She had moderate ankle and sacral edema, and bilateral crepitations at her lung bases. The apex beat was in the eighth left intercostal space in the posterior axillary line. A very loud systolic murmur accompanied by a thrill was audible down the left sternal edge and was heard well also at the apex. The second

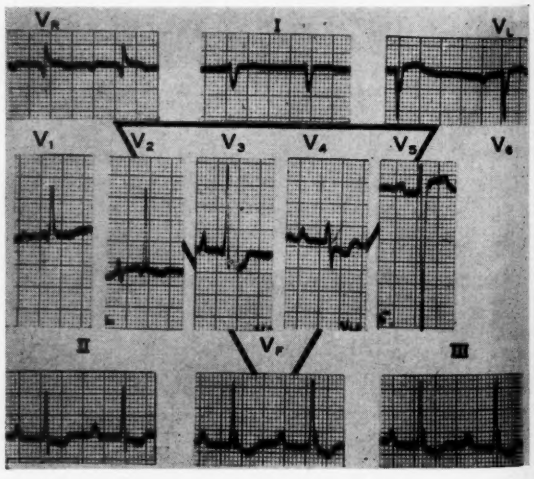

Fig. 4. Electrocardiogram of patient with tetralogy of Fallot, showing P pulmonale and right ventricular dominance.

Fig. 5. View into the right ventricle of heart with the tetralogy of Fallot, showing the right ventricular hypertrophy, the ventricular septal defect (*lower arrow*), and the right ventricular outflow tract (*upper arrow*), with the cone-shaped pulmonary valve above.

sound was faint and single. No abnormality was found in the other systems.

Laboratory findings included a hemoglobin of 18 Gm. per 100 ml., hematocrit of 56 per cent, and sedimentation rate of 1 mm. in 1 hour. The electrocardiogram (Fig. 4) showed at least moderate right ventricular dominance, prolongation of the P-R interval, and P pulmonale. The chest roentgenogram confirmed the presence of gross cardiac enlargement and displayed a right-sided aortic arch.

Mental confusion and apathy were the outstanding features of her condition. Although the signs of congestive failure largely cleared with digitalis and diuretics, her condition gradually deteriorated. During the 6 weeks of her stay in hospital she experienced a series of collapses in which she became gray in color, her blood pressure fell, and she remained comatose for as much as 2 days. On two occasions these attacks were precipitated by being sat up out of bed. She died in coma 6 hours after the onset of one of these attacks.

At postmortem examination the heart weighed 512 grams. Both ventricles were hypertrophied; the average thicknesses of the right and left ventricular walls were 14 and 18 mm., respectively (Fig. 5). The aorta overrode a high interventricular septal defect, 14 mm. in diameter, so that two thirds of the aortic opening faced the right ventricle.

The pulmonary valve (Fig. 6) showed fusion of the thickened cusps to form a dome-shaped diaphragm with a central opening which measured 10 by 8 mm. There was no infundibular stenosis. The main pulmonary arterial trunk and both branches were dilated; the walls of the vessels were of normal thickness. The ductus arteriosus and the foramen ovale were both closed. The aortic and mitral valves were normal. The coronary arteries were patent and in the normal anatomic situation. The pulmonary veins and venae cavae were normal.

Discussion

Twenty of the reported cases of Fallot's tetralogy with survival of the patients to over the age of 40 years have been studied.

Of the patients whose ages were stated, 3[15,26,28] were over 60 years, 10 were between 50 and 60 years,[14,17,18a,22,25,27a,b,29,30a,31] and 9 were over 40 years.[16,18b,19,20,21,23,24,28b,30b] The oldest was a 69-year-old man,[26] and the oldest woman whose case was previously reported was 64 years of age.[28a] Only 4 patients, aged 56,[31] 53,[30a] 52,[27b] and 45,[21] were alive when their cases were reported.

Ten patients were males, 7 were females, and in three reports the sex was not stated.

Six patients[18b,20,25,27a,b,28a] were cyanosed at birth, and 4[14,17,22,28b] had been blue as long as they could remember. One patient[31] was known to be cyanosed at 32 years of age and was moderately cyanosed when he was reported alive at 56 years. Three patients did not develop cyanosis until middle life: in one,[30a] cyanosis appeared after pulmonary tuberculosis; another[24] became cyanosed at the onset of congestive failure 3 years before his death; and the third[26] developed cyanosis intermittently in middle age and was only slightly cyanosed at the

Fig. 6. The pulmonary valve of heart with the tetralogy of Fallot, seen from above. The forceps are behind the valve leaflet.

time of his death. In 2 other cases[16,18a] the age of onset of cyanosis is not given: both patients were cyanosed at the time of death. One patient[29] was never cyanosed, even at the time of death. It was not possible to find a relationship between the severity or age of onset of cyanosis and the length of survival. Certainly the patient[26] who survived the longest was a man (aged 69) who became cyanosed only intermittently after middle age. On the other hand, one patient[28a] who had marked cyanosis and clubbing died at the age of 64 years, and our patient who had been cyanosed as long as she could remember lived to 68 years.

Clubbing was present in 15 patients, and, where graded, was marked in 5,[14,17,20,22,28b] moderate in 2,[25,31] and slight in 1.[18a] There was no clubbing in 2 patients,[26,29] and the presence or absence of clubbing was not mentioned in the other reports. The degree of clubbing was closely paralleled by the intensity of cyanosis and by the height of the red blood cell count. All 5 patients with marked clubbing were cyanosed from their early youth.

Most patients were very much limited by shortness of breath, but nevertheless were capable of a wide range of activity. Two[27a,30b] were always dyspneic at rest. Two[14,28a] were dyspneic with slight exertion: one of these was a musician who had also worked as a printer and a clerk, and who undertook a trip from America to Europe. Five[16,17,18a,b,31] were dyspneic only with greater exertion; 2 of these worked as laborers, one also as a coal miner and building superintendent. One was a manageress of a restaurant, and one was an accountant. Eight patients whose effort tolerance was not defined[20,22,24,25,26,28b,29,30a] followed various occupations, including those of an electrical engineer, a seamstress, a journalist, a racing driver, and a night watchman whose duties involved climbing seven flights of stairs nightly. One of these[28b] had played football as a boy; another[26] described himself as "quite a runner" in his day. One patient[27b] when first reported upon at the age of 26 years was "always short of breath," but when described again at 52 years was "not unduly dyspneic." A number of patients had successfully undergone operations, including tonsillectomy, cholecystectomy, tooth extraction, sterilization, and orthopedic operations. One[26] underwent electroconvulsive therapy, and one woman had had two normal confinements, at 32 and 35 years of age.

The presence of cyanosis and the degree of dyspnea were not necessarily related. For example, 2 patients[26,29] who showed no clubbing or polycythemia, and who developed cyanosis either late or not at all, had both been dyspneic as long as they could remember and had become very dyspneic with effort. On the other hand, 2 patients[16,18a] who were capable of heavy work and who had been laborers were both cyanosed and had clubbing of the fingers. Donzelot[21] also, after studying 200 cases of the tetralogy of Fallot, commented that no close parallel between the degree of cyanosis and dyspnea could be found.

Lian and Fleury[22] remarked that their patient had noticed improvement in her effort tolerance with the onset of puberty, and that her condition had gradually deteriorated after the age of 40. One of Soulié's patients[30] became less cyanosed at about 15 years of age. Bedford[27b] describes a patient who was less dyspneic at 52 years of age than she had been at 26, and the patient here reported said that she became less dyspneic after the age of 17, at which time she learned to ride a bicycle. On the other hand, Donzelot[21] found that puberty was a critical time for these patients and sometimes heralded deterioration and death.

Although 4 patients[25,28a,29,31] had no complaints other than shortness of breath on effort and cyanosis, cerebral complications and congestive episodes were common. Nine patients[16,18a,b,20,22,23,24,26,27a] suffered congestive cardiac failure which varied in severity from ankle edema to gross congestion. In one patient,[18b] recurrent attacks of congestive failure were associated with episodes of coma and transient neurological abnormalities. Hemiplegia developed in 4 patients,[14,18b,25,26] and 5 patients[14,18b,20,27a,28b] had symptoms of episodic cerebral ischemia which produced transient paresthesia and weakness of the limbs. It seems likely that these attacks were embolic or thrombotic in origin, and this tendency was demonstrated in 2 other patients, one of whom[28b] developed a popliteal embolus and a pulmonary infarct, and the other[29] a femoral vein thrombosis.

The most common mode of death was coma. In 5 patients[18a,b,20,22,27a] this was associated with congestive failure, and 2[14,26] died after strokes. One patient[28a] went into anoxic coma without congestive cardiac failure after a respiratory infection. One[25] developed a right hemiplegia and congestive failure 4 days after operation for relief of a gallstone ileus. One[16] died at the age of 41 years of chronic glomerulonephritis, one[29] at 53 years of chronic pyelonephritis, secondary to a carcinoma of the uterine cervix, and one[23] at 47 years from carcinomatosis originating in the bladder. One[28b] had a pulmonary infarct at 47 years of age after a leg was amputated for a popliteal embolus. One patient[24] died suddenly, an unexplained death. Two deaths[17,30b] were not detailed, and 4 patients were still alive when their cases were reported.

In only 10 cases were the radiologic appearances described. In 8 cases,[14,16,18a,b,22,27a,b,29] cardiac enlargement was demonstrated, and one heart[31] was not radiologically enlarged.

At postmortem examination the hearts were all enlarged; the weights ranged from 370 to 970 grams, the former figure being in a woman. The average weight was 606 grams. The maximum thickness of the free right ventricular wall ranged from 10 to 20 mm. (average of 10 = 15.7 mm.), and that of the left ventricular wall also ranged from 10 to 20 mm. (average of 9 = 15.8 mm.).

The pulmonary stenosis was valvular in 5 hearts,[17,20,25,27a,28a] infundibular in 5,[16,23,26,28b,29] and a combination of the two in 5.[14,18a,b,22,30b] One pulmonary artery[24] ended blindly 1 cm. from the pulmonary valve; the pulmonary blood supply was through a patent ductus arteriosus. The lumen of the outflow tract ranged from 12 to 240 sq. mm. in 6 valves and from 30 to 390 sq. mm. in 6 infundibula. A striking feature was the frequency of bicuspid pulmonary valves; 10 hearts showed this variation.

The area of the ventricular septal defects ranged from 78 to 1,500 sq. mm. in 11 cases; one other[22] admitted a thumb, 2[17,30b] admitted two fingers, and 2[28a,b] were described as "large."

The degree of overriding of the aorta was estimated in various ways: in 3 hearts[18a,26,30b] there was one-third overriding; in one[20] the aorta overrode the left ventricle more than the right; in one[25] the aorta arose from the right more than from the left; in 2[14,18b] there was two-thirds overriding; and in one[16] the aorta arose entirely from the right ventricle.

A number of associated cardiac malformations were noted: in the case[12] in which the pulmonary artery terminated in a blind end above the valve, the ductus arteriosus carried blood to the lungs. In no other case was the ductus patent. The foramen ovale was present in 4 hearts; it was described as "slit-like" in 1, and in the other 3[16,18b,28a] was accompanied by a valve which was apparently capable of anatomic closure. In one heart[16] the aortic valve had four cusps, and in another[29] it was bicuspid. Calcific aortic stenosis was present in one case,[30b] accompanied by tricuspid calcification and atheroma of the aorta. A right-sided aortic arch was seen in 2 patients.[27a,b]

There was a wide range of severity of heart deformity in these patients with Fallot's tetralogy, but no constant relationship could be found between the degree of deformity and longevity of the patient. The severity of symptoms during life could not be correlated with the anatomic findings, nor did the degree of right ventricular hypertrophy relate to the size of the septal defect or to the lumen of the pulmonary valve. For example, of 2 hearts of similar weight and with a septal defect of the same size, that which had the largest pulmonary passage and the least aortic overriding had the greatest degree of right ventricular hypertrophy. The anatomic findings could not be correlated with the severity of clubbing or polycythemia.

Summary

With the development of surgical techniques which allow correction of most congenital heart defects the opportunity to study the natural history of these lesions is being lost. Geriatric units are possible sources of instances of long-term survivals. Two cases of cyanotic congenital cardiac disease are reported from a geriatric unit. One patient with the tetralogy of Fallot who survived to the age of 68 years is believed to be the oldest woman whose case has been reported. The other patient who

survived to 71 years had the trilogy of Fallot. A review is made of previous reports of survival beyond the age of 40 years of patients with these conditions.

I should like to thank Dr. J. L. Newman for permission to report these cases, and Dr. J. C. P. Williams for assistance with presentation.

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*References 14-31 show the reported cases of tetralogy of Fallot with survival over 40 years of age, with sex and age of the patient given.

Clinical pathologic conference

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Clinical abstract

History. An 11-year-old boy was first admitted to Cleveland Clinic Hospital on Dec. 17, 1955, because of dyspnea. He had been in apparent good health until 1 year before admission, when he had an acute illness characterized by fever, headache, and aching in both thighs. These symptoms persisted for 1 month before he was hospitalized, in another institution.

On admission there his temperature was 103.6°F. and his pulse rate was 120. The heart was enlarged and a loud systolic apical murmur was noted. A questionable diastolic murmur was recorded. The urine was normal, the erythrocyte count was 3,350,000 per c.mm., the hemoglobin 10.5 Gm. per 100 ml., and the leukocyte count was 15,750 per c.mm., with a differential count of 71 per cent polymorphonuclear leukocytes, 1 per cent band cells, 26 per cent lymphocytes, 1 per cent monocytes, and 1 per cent eosinophils. The results of spinal fluid studies and blood cultures were normal. An electrocardiogram showed a P-R interval of 0.19 to 0.20 second and "a tendency toward right axis deviation." A roentgenogram of the chest revealed evidence of a "grossly enlarged heart." Treatment with penicillin, cortisone, and aspirin was instituted, and within 4 days his temperature was normal. Penicillin therapy was continued for 13 days. Six days after discontinuance of penicillin, his temperature had risen to 104.6°F., and the use of the drug was resumed. Within 18 hours his temperature was normal. Penicillin was given daily for 4 days and twice weekly thereafter. Cortisone was continued until March 9, 1955, and he was discharged from the hospital on March 21, with instructions to rest at home; prophylactic penicillin was to be continued.

He was admitted to the hospital because of a cough, in June, 1955, and again on July 5, 1955. Radiographic examination revealed enlargement of the heart, and the shape was thought to be suggestive of a pericardial effusion. The cough cleared rapidly with the use of a low-salt diet, digitalization, and the administration of mercurial diuretics. Penicillin was administered during and after hospitalization, and digitalization was maintained. Subsequently, he was reported to have had "occasional pulmonary edema" that responded well to the use of mercaptomerin sodium and acetazoleamide. On Nov. 29, 1955, he was lethargic and his face was edematous, although there was no edema elsewhere. Tests showed hyaline casts in the urine; hemoglobin, 8.5 Gm. per 100 ml.; and a leukocyte count of 12,900 per c.mm. The electrolytes were normal but the nonprotein nitrogen was 67 mg. per 100 ml. He improved slowly with diuretic therapy and was transferred to Cleveland Clinic Hospital on Dec. 17, 1955.

Physical findings. On admission, his temperature was 98.4°F., the pulse rate was 116, and the blood pressure was 118/78 mm. Hg. He was well developed but thin. There was a prominent precordial bulge. The heart appeared to be considerably enlarged. A striking apical systolic thrill was palpable. The pulmonic second sound was accentuated. There was a Grade 5 apical systolic murmur: this murmur was transmitted to the back, the forearms, and even to the patellae. A Grade 1 or Grade 2 early blowing diastolic murmur was heard along the left border of the sternum. The spleen was palpable, but the liver was not palpably enlarged.

Laboratory findings. The results of tests were: normal urine; hemoglobin, 12.3 Gm. per 100 ml.; the hematocrit reading, 42 ml., and leukocyte count, 5,300 per c.mm. The serum electrolytes were normal, and the blood urea was 27 mg. per 100 ml. A corrected erythrocyte sedimentation rate was normal; tests were negative for C-reactive protein, and for lupus erythematosus. The electrocardiogram is shown in Fig. 1,*A*. Roentgenograms (Figs. 2*A-C*) of the chest showed evidence of enlargement of all chambers of the heart, and on fluoroscopic examination there was intrinsic pulsation in the hilar vessels.

Course. The patient was discharged on the fifth hospital day and was readmitted on Jan. 2, 1956, for cardiac catheterization and cineangiocardiography. The right ventricular pressure was 72/2 and the pulmonary arterial pressure 75/46 mm. Hg.

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Received for publication Aug. 16, 1960.
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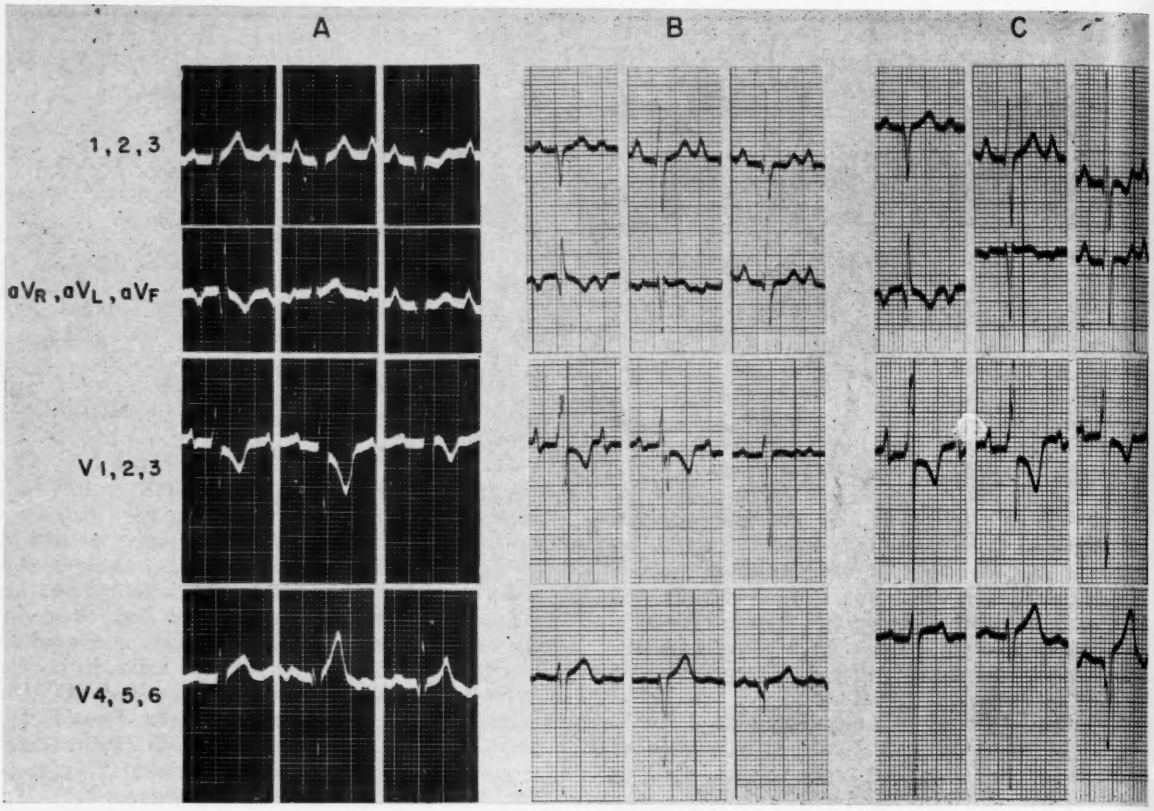

Fig. *1*. Electrocardiograms. *A*, December, 1955. *B*, Aug. 1, 1957. *C*, May 20, 1958.

The wedge pressure was 22 mm. Hg. No evidence of a shunt could be demonstrated by oxygen saturations or cineangiocardiography. He was discharged to return to a schedule of bed and chair rest at home. He was given a low-salt diet, digitalis, and Gantrisin daily. One year later he was re-examined and seemed to be much improved; he had no complaints. Examination showed no significant changes from the previous findings except that the spleen was not palpable. A roentgenogram of the chest showed that the transverse diameter of the heart had increased 2.5 cm. in the 13 months since the time of his previous studies. He was examined again on Aug. 1, 1957, because of dyspnea during rapid walking and a few attacks of paroxysmal nocturnal dyspnea. Examination showed no significant changes from the previous findings except that there were a few râles present at the base of the right lung. An electrocardiogram is shown in Fig. 1,*B*.

On May 20, 1958, he was examined because of mild dyspnea and a history of having had an episode of severe dyspnea, abdominal pain, and "liver swelling." Râles and rhonchi were heard in both lung fields, but there were no other significant deviations from the previous physical findings. An electrocardiogram is shown in Fig. 1,*C*. It was decided to recheck cardiac catheterization and cineangiocardiography in order to determine the presence or absence of a shunt. He was readmitted to the hospital July 6, 1958. He was dyspneic and edematous on admission, and cardiac catheterization was deferred because of the presence of congestive heart failure. An electrocardiogram was similar to that of May 20, 1958, except that atrial fibrillation had developed. Roentgenograms of the chest (Figs. 3*A-C*) showed evidence that the heart had increased in size, the transverse diameter being 18.2 cm. During the following night when he arose from bed to use a urinal, he fell, and died immediately.

Discussion

DR. PROUDFIT: Mitral insufficiency appears to be the predominant lesion in this case. The physical findings are consistent with that diagnosis. Mitral insufficiency of marked degree may be manifest by a loud systolic murmur that is widely distributed. There was radiologic evidence of left atrial and left ventricular enlargement. No mention was made of systolic expansile pulsation of the left atrium. The pulsation of the hilar vessels is peculiar and may represent pulsation in the pulmonary veins, especially in view of the fact that no cause for high pulmonary blood flow was demonstrated. The catheterization findings are suggestive of mitral insufficiency. Finally, atrial fibrillation developed late in the course of the disease.

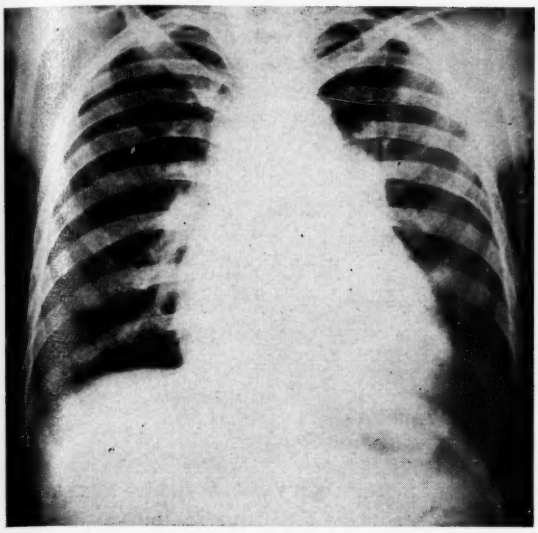

Fig. *2A*. Posteroanterior chest film taken on Jan. 4, 1956.

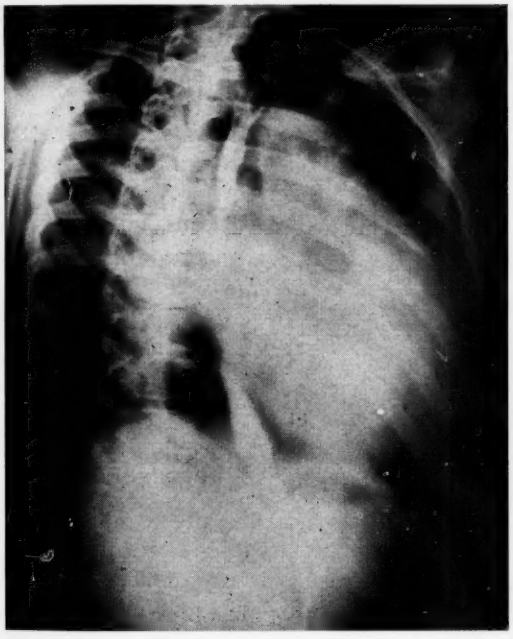

Fig. *2B*. Right anterior oblique chest film taken on Jan. 4, 1956.

The electrocardiograms in this case are interesting. The reported "tendency toward right axis deviation" in the electrocardiogram taken 1 month after onset of his acute illness suggests the presence of long-standing disease. Our original record (Fig. 1,*A*) shows notched high-voltage P waves, a P-R interval of 0.2 second, right axis deviation, and large R waves with delayed intrinsicoid deflections in Leads V_1 and V_{3R}. These findings are indicative of enlargement of both atria and right ventricular hypertrophy. Leads V_5 and V_6 show interesting changes. There is a Q wave before a small R wave in Lead V_5, and a slurred Q wave before a small R wave in Lead V_6. The intrinsicoid deflection is delayed in Lead V_6. There were inverted U waves in Leads V_4, V_5, and V_6; these may be seen in left ventricular hypertrophy. The inverted U waves persist in subsequent records. An electrocardiogram of Aug. 1, 1957 (Fig. 1,*B*) shows decreasing voltage of the R waves in Leads V_5 and V_6 and a delayed intrinsicoid deflection in Lead V_6. In the record of May 20, 1958, the R wave is absent in Lead V_6—a finding seen occasionally in severe right ventricular hypertrophy.

The cause of the mitral insufficiency is the real diagnostic problem. In the differential diagnosis, rheumatic valvulitis, perforation of a leaflet, or rupture of a chorda tendinea as a result of bacterial endocarditis and congenital deformity involving the mitral valve must be considered. The history of the acute illness is not typical of rheumatic fever. There was a systolic murmur present at the time of the patient's first medical examination. Unfortunately, it was not noted whether a precordial bulge was present then, although it was stated to

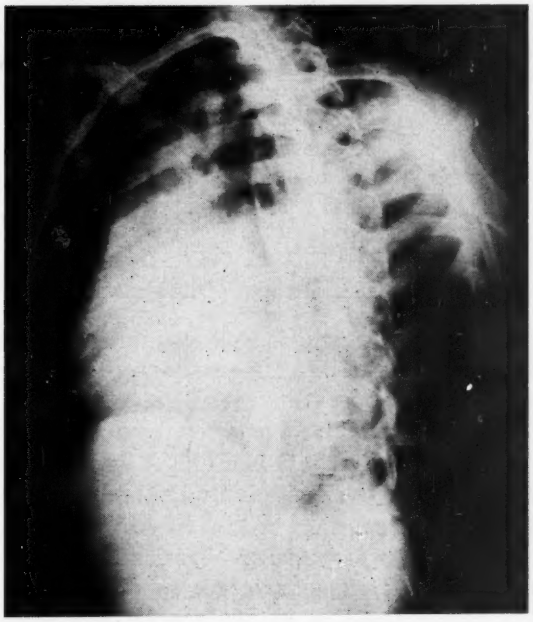

Fig. *2C*. Left anterior oblique chest film taken on Jan. 4, 1956.

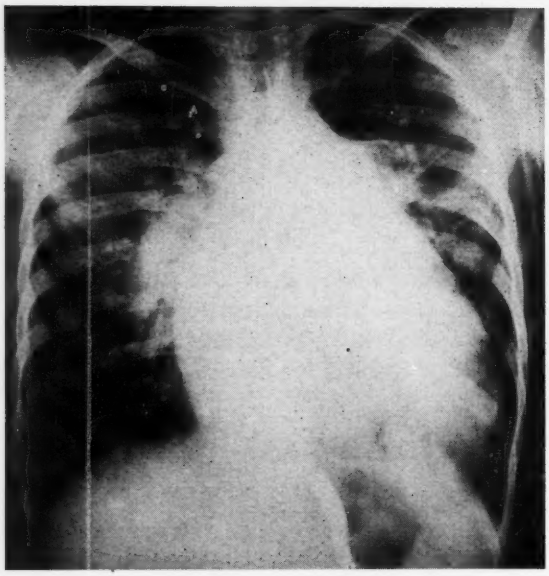

Fig. *3A*. Posteroanterior chest film taken on May 21, 1958.

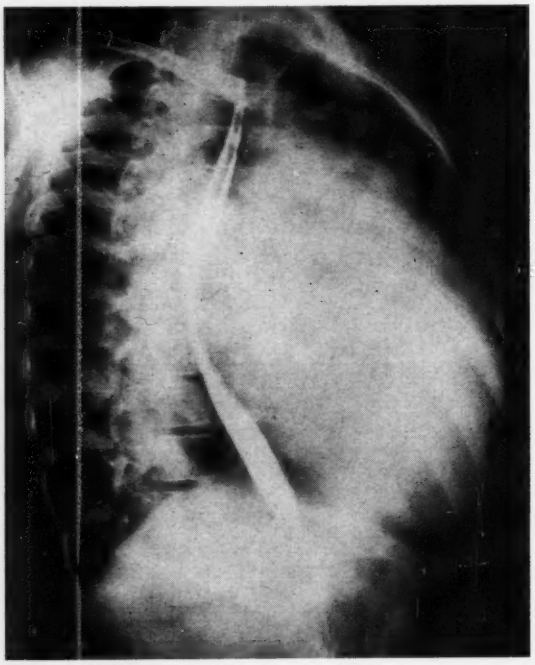

Fig. 3*B*. Right anterior oblique chest film taken on May 21, 1958.

be present subsequently on admission to Cleveland Clinic Hospital. A precordial bulge would have indicated long-standing cardiac disease and would have been consistent with congenital heart disease or rheumatic heart disease acquired earlier in life. The evidence of a "greatly enlarged heart" on radiographic examination at the time of the original study must indicate long-standing disease, severe myocarditis, or pericardial effusion. There is nothing to suggest strongly the latter possibility. The absence of notation of the usual criteria for diagnosis of active rheumatic fever is disturbing. It seems likely that if he had had acute rheumatic myocarditis, he must have had pre-existing rheumatic heart disease, in view of the fact that he had marked cardiac enlargement and right axis deviation in the electrocardiogram at the time of his original examination, even though his illness had been of short duration. Congestive failure was an early and rather persistent manifestation until death. It would seem to be necessary to assume that this boy had previous rheumatic heart disease if the illness was of rheumatic origin, and that the terminal illness was due to recurrent disease with active myocarditis. It is difficult to be sure that myocarditis was present, however. A firm support for the diagnosis of rheumatic heart disease cannot be established.

It is possible that this patient had acute bacterial endocarditis to account for his original illness, although later blood cultures were negative. Acute endocarditis can cause perforation of the mitral valve

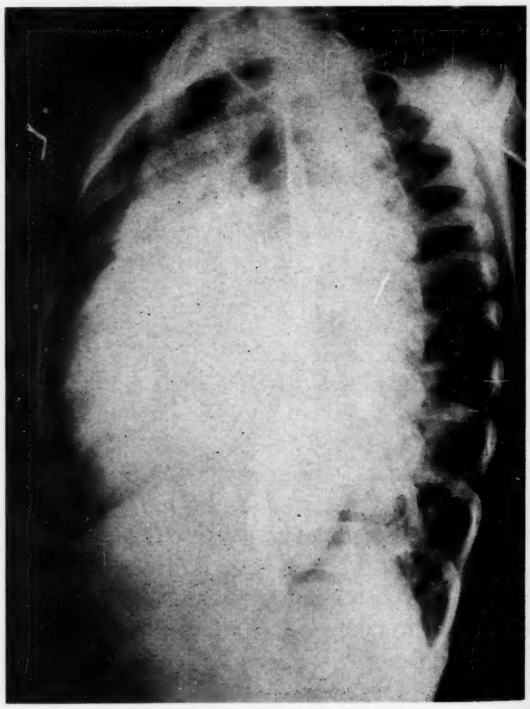

Fig. 3*C*. Left anterior oblique chest film taken on May 21, 1958.

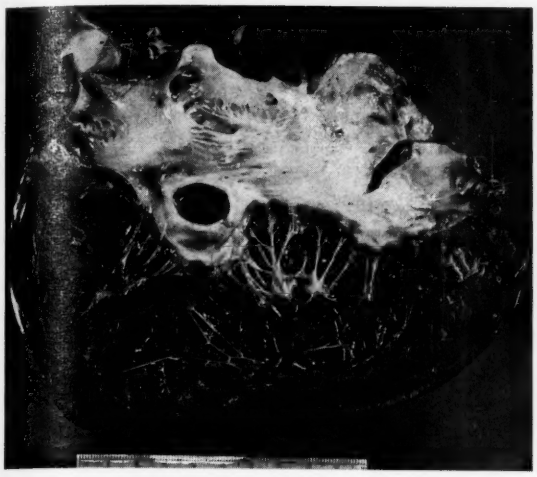

Fig. 4. Photograph of gross left atrial and ventricular chambers, showing the large fenestration in the anterior leaflet of the mitral valve.

or rupture of a chorda tendinea, resulting in mitral insufficiency. This could account for the development of congestive heart failure, which was a subsequent problem. It is possible that he had a penicillin-sensitive organism and that he received sufficient treatment to arrest the infection even though treatment was not intensive. The presence of severe cardiac enlargement and the electrocardiographic changes early in his illness are important evidence against this diagnosis.

Congenital mitral insufficiency as an isolated lesion is rare. It seems likely that this boy did not have any atrial septal defect or valvular lesion of congenital origin. Most commonly, mitral insufficiency is associated with septum primum defects. Certainly, the possibility of congenital mitral insufficiency cannot be excluded. It would be difficult to explain on the basis of congenital disease the acute illness that heralded his disease clinically. On the other hand, the extreme cardiac enlargement and electrocardiographic changes present early in the illness, the precordial bulge noted later, and the relentless course of his disease would be consistent with congenital heart disease.

In conclusion, mitral insufficiency is the structural lesion of the heart. The valvular defect may have been of rheumatic or of congenital origin. Although there was no certain evidence of rheumatic myocarditis, I think that the insufficiency is more likely to have had a rheumatic than a congenital basis.

DR. MCCORMACK: Many of you will remember that some months ago we presented an unusual cause of aortic insufficiency resulting from rupture of a semilunar valve. I could not resist presenting another unusual case of valvular insufficiency involving, in this instance, the mitral valve.

The heart was globular and much enlarged; it weighed 640 grams. The epicardium was everywhere glistening and transparent. The globular shape was in part due to an enlarged right ventricle. When the heart was opened, the right ventricle and both atria were markedly dilated. The myocardium was reddish-brown and firm. The right ventricle varied from 0.1 to 0.3 cm. in thickness, and the left ventricle at its maximum measured 1.3 cm. in thickness. The aortic, tricuspid, and pulmonary valves were normally formed, thin and without distortion. The anterior leaflet of the mitral valve was remarkable (Fig. 4). Near its base was a round fenestration which measured 1.5 cm. in diameter. The edge of this fenestration was slightly thickened, but there was no evidence of any attachments to it. The remainder of the mitral valve was normal anatomically, with delicate, pliable margins and thin, discrete chordae tendineae. Scattered over the walls of the left atrium, both in the region of the valve and on the posterior surface, were numerous endocardial thickenings, representing multiple so-called "jet lesions." Some of these were scimitar-shaped, but others represented mainly endocardial thickening. Microscopically, there was no evidence of any pre-existing rheumatic heart disease in so far as changes in the atrioventricular angle, vascularity of valves, or myocardial scarring were concerned. The cardiac fibers were slightly enlarged and possessed large angular nuclei.

The lungs weighed 1,000 grams and were firm and slightly brown. Microscopically, they showed all the features of chronic passive congestion; the pulmonary vasculature was only slightly increased in prominence. The liver also showed the features of chronic passive congestion.

I should, then, at least attempt to explain the presence of the perforation within the anterior leaflet of the mitral valve. There

are three possibilities for this occurrence. The one that I slightly favor is that it represents a congenital failure of formation of the valvular leaflet. The lesions that most resemble this physiologically, and possibly anatomically, are those that occur in association with a persistent ostium primum defect. The changes in the mitral valve in those instances, however, usually are manifested as clefts in the valve, with free margins that may or may not be bound to the ventricular wall by shortened chordae. It is a lack of recognition of these clefts that may be responsible for mitral insufficiency after complete repair of the septal defects present. The second possibility, also congenital, is a variation of the anomaly, double orifice of the mitral valve. However, no signs of leaflets or accessory chordae tendineae were found. A third possibility would be that of a most unusual form of healed bacterial endocarditis, with the point of bacterial lodgment being high on the valve rather than along the valve margins as usually seen. However, nothing in the clinical history prepares us for this eventuality, and, if such is the case, it is a most fortuitous set of circumstances. A lack of vascularity and other signs of previous inflammation also lessens the possibility of such an origin. In any event, there were no stigmata of previous rheumatic heart disease that we could demonstrate.

To summarize then, the anatomic findings in this case are: idiopathic fenestration of the mitral valve with associated jet lesions and marked cardiomegaly, resulting in severe mitral insufficiency. Evidences of cardiac failure were found in the lungs and liver in the form of chronic passive congestion.

Diagnosis: Valvular insufficiency due to idiopathic fenestration of the mitral valve.

Annotations

Patent ductus in infancy

Many children present with symptoms of cardiac failure in the first year of life, and a proportion of these will be found to be suffering from patent ductus arteriosus. It is important to distinguish this group, since prompt operation can be both lifesaving and curative. These children frequently present with feeding difficulties, failure to thrive, or as "breathless babies," and it is not until a careful examination of the chest is undertaken that the presence of a cardiac murmur focuses attention on the heart as a possible cause of the symptoms.

Evidence of some degree of congestive failure, such as increase in venous pressure, hepatomegaly, or obvious dyspnea at rest, is very frequently present. When such signs are found, intensive medical therapy should be initiated without delay, and operation should be deferred until the cardiac failure has been adequately controlled with appropriate medical therapy. Not infrequently an infection of the respiratory tract initiates cardiac decompensation, and, when there is any suggestion that this is so, appropriate antibiotic therapy should be commenced without delay. In general, these children show a prompt and gratifying response to treatment, and one can then proceed to operate, but it is most unwise to undertake operation in these cases before controlling any degree of cardiac failure which may be present.

In this age group the auscultatory findings are rarely typical, and the presence of a fully developed continuous murmur is unusual. Reliance must be placed on the peripheral signs. The presence of palmar pulsation and of a wide-amplitude peripheral pulse is always very suggestive of the presence of a patent ductus arteriosus. The electrocardiogram will usually show evidence of left ventricular strain, unless pulmonary hypertension or some other complication is also present, and radiography will demonstrate marked cardiomegaly with obvious evidence of a substantial left-to-right shunt. In general, no additional investigations should be carried out in these cases, since the children are usually seriously ill and to undertake such procedures as angiocardiography or cardiac catheterization may well militate against survival.

We have always adopted the attitude that if a patent ductus cannot be reasonably excluded on clinical examination, these children should be submitted to exploratory thoracotomy. In practice, reliance on the peripheral signs and a careful appraisal of the clinical signs that are present will usually result in a correct diagnosis by an experienced cardiologist.

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Erythrocytosis and ischemic myocardial disease

It is generally recognized that both venous and arterial occlusions occur frequently in polycythemia vera. Coronary artery thrombosis has been reported in from 6[1] to 25 per cent[2] of patients with this disease, and treatment with radioactive phosphorus is said to decrease the incidence of coronary thrombosis.[2] This would suggest that the association of coronary thrombosis and polycythemia is not mere coincidence. The patients reported in the literature usually have well-established erythremia. Yet there are patients in whom moderate erythrocytosis exists in association with coronary artery disease, and in whom the erythrocytosis is usually ignored. In this group of patients it is difficult to know what influence the erythrocytosis has on the production or the course of myocardial ischemia. The increased viscosity of the blood would be expected to place a stress on the heart and result in some impairment to coronary flow. Possibly in part because of the increased viscosity of the blood, many of these patients have mild arterial hypertension.

Examination of the clinical records of such individuals suggests that the erythrocytosis has an adverse effect on coronary blood flow. We have recently evaluated 12 patients with coronary artery disease and packed red cell volumes ranging between

50 and 54 per cent (mean, 51 per cent). The patients ranged in age from 39 to 66 years (mean, 47 years); 5 were less than 45 years. All had angina and 3 had clinical and electrocardiographic evidence of myocardial infarction. The hematocrit was lowered to within normal levels by venesection in 3 of the 12 patients, and there was definite clinical improvement in each patient, in that the frequency of the anginal attacks decreased. In one of the 3 patients with arterial hypertension in addition to erythrocytosis the blood pressure fell to normal after venesection.

Although all of the patients were in the arteriosclerotic age group, the fact that half of them were less than 45 years of age may be of significance. The etiology of the erythrocytosis was not always evident. The other formed elements of the blood were not increased, although minimal splenomegaly was present in 3 patients. In one of the 12 patients the polycythemia was probably secondary to pulmonary disease. The bone-marrow was studied in 2 patients and was found to suggest early polycythemia vera. No definite etiology for the erythrocytosis was apparent in the other patients. Whether or not they represent instances of early or mild polycythemia vera or merely normal variation in erythrocyte values is not known. Whatever the etiology, it appears that even moderate erythrocytosis exerts a deleterious effect on the cardiovascular system of some individuals. Thus, in the cardiac patient it is probably wise to consider the erythrocyte concentration and to reduce even a moderately elevated hematocrit to mean normal levels, that is, to about 45 per cent. Detailed clinical studies of such patients are needed in order to determine the extent to which moderate erythrocytosis may produce myocardial ischemia.

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Reliability of the indicator-dilution technique

Though an isolated measurement of cardiac output has little specific diagnostic value, it is an important physiologic variable, the use of which permits the calculation of such parameters as stroke work, stroke volume, stenotic valve areas, and total peripheral resistance. When the dye-dilution method is employed to measure flow, additional data may be derived, such as the mean transit time and a number of "central" blood volumes—depending upon which pair of injection and collection sites is used. The wide popularity of this technique in recent years is related to its convenience, applicability to many types of sick and well patients, and its suitability for use in transient "steady states." Many reports of studies in which the dye curve was utilized are prefaced by justifying statements, holding that the cardiac output measured by this method is reproducible, accurate, and that it checks well with those determined by the Fick principle. Although the literature reveals no systematic difference, there is little evidence to support an argument for a high degree of reproducibility, accuracy, or consistent checks against the Fick method.

Two hundred and seventy-eight tabulated pairs of cardiac outputs as measured by the Fick and indicator-dilution techniques of various types, both in human beings and dogs, have been reviewed from the literature.[1-9] Analysis of these comparisons reveals that two standard deviations of the differences is ±40 per cent of the mean cardiac output for the group. Similarly, there are 241 graphed but not tabulated pairs, and the scatter of these differences is of the same order of magnitude.[10-13] The nature of this variability can be found in an analysis of 36 tabulated and 31 graphed indicator-dilution studies done in duplicate.[2,4-7,13,14] This demonstrates that the dye method is reproducible only to ±24 per cent (two standard deviations). A similar error is said to exist for the Fick method.[2] The explanation for the poor reproducibility of the cardiac output by the dye-dilution technique probably resides in both methodological errors and changes in the patients' state between determinations. Unfortunately, there has been little published regarding the magnitude of either of these factors. In their classic combined study in 1948, Hamilton, Cournand, and their respective groups reported variations of weighing and pipetting that could result in a 6 per cent error if each were in the same direction.[2] More recently, duplicate cuvette densitometry has been used in man to record 266 paired curves after a single injection of indicator from the same and different arteries.[15] These studies have shown that a two standard deviation variation from the same artery was ±450 c.c. per minute. On the assumption of a mean cardiac output of 6 L. per minute this variation would be approximately ±8 per cent. The variability of the cardiac outputs calculated from curves recorded at different arteries after a single injection of indicator was more than twice this value. These data suggest that errors in instrumentation and variations associated

with injection, collection, and incomplete mixing of the indicator can account for more than half of the observed variation in reproducibility. The remainder must be attributable to lack of a "steady state" in man, and the known changes in cardiac output in anesthetized animals.[16] Reduction of the total variation is difficult and involves the improvement of already advanced technical methods. Equally difficult is the achievement of greater patient stability. This latter may tax the personal skill of the investigator, who, to reach this end, must take the emotional as well as the radial pulse of his subject.

The disturbing "coefficients of variation" mentioned above are well known, grudgingly tolerated, and not well publicized by workers in the field, possibly because there is nothing better at the moment to supplant the technique. The errors inherent in the dye-dilution method necessitate that changes in cardiac output and all other mathematically related parameters be large in order to have any significance, and make these measurements relatively insensitive to small changes. Thus, studies in this area may have to deal with trends rather than "p" values until something better becomes available.

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The venous hum

Although mentioned in most textbooks of cardiology, the venous hum is perhaps the least studied of cardiovascular acoustic phenomena. It is important not only because of the high incidence of its occurrence in children (over 50 per cent in some series[1,2]), but because it may easily be confused with murmurs of significant cardiac lesions when the hum in the neck is transmitted downward over the upper chest. Under these circumstances, unless diagnostic maneuvers designed to obliterate the venous hum are performed, a diagnosis of patent ductus arteriosus or even aortic insufficiency may

be mistakenly entertained.[3] In addition, the detection of a venous hum may alert the clinician to the possibility of anomalous pulmonary venous drainage into the caval system.[4,5]

Venous hums are best heard over the right supraclavicular area, but they can occur over both sides of the neck, or solely over the left jugular vein. They are loudest in the upright position, during inspiration, and when the veins are put on the stretch by turning the head to the opposite side. The hum disappears with pressure over the jugular vein or on assumption of the supine position. The murmur is continuous, and has a cavernous or roaring quality, the pitch of which may be altered by light pressure with the stethoscope. Intensity of the murmur increases during diastole, a feature distinguishing the venous hum from the murmur of an arteriovenous aneurysm or a patent ductus arteriosus. When venous hums are transmitted downward over the precordium, these precordial components can be eliminated by pressure over the right side of the neck, and this procedure should be carried out whenever a continuous murmur is heard over the chest.

The exact mechanism whereby the venous hum is produced is not completely understood. The diminished viscosity of the blood in the case of anemia favors its appearance. Its frequent occurrence in young children and its accentuation by inspiration or the upright position indicates that factors leading to an increase in the velocity of blood flow in the great veins of the neck are primarily responsible for the hum. Other "flow murmurs" apparently due to increased velocity of blood flow have been demonstrated by intracardiac phonocardiography.[6] Placing the neck veins under tension increases the intensity of the hum, suggesting that partial venous constriction is a contributory mechanism. Anatomic determinants also play an important role in the genesis of the venous hum, since the site of origin of the bruit is at the convergence of several streams of fluid entering the superior vena cava. This may favor the initiation of periodic wake fluctuations, capable of generating sound vibrations well above the threshold of audibility.[7] In summary, increased velocity of blood flow, diminished viscosity of the blood, partial venous constriction, and anatomic factors leading to wake fluctuation are operative, singly and in combination, in producing the venous hum.

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Letters to the Editor

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March 6, 1961

To the Editor:

These are the impressions of an American physician on diet, coronary atheromatosis, and related problems in East Africa, as gathered on a short trip through Africa.

During the past several years I made three trips to South and East Africa; as usual, I spent some time in visiting hospitals, clinics, prominent internists and pathologists, etc., with my special interest being in cardiovascular diseases. About two years ago I published a description of my findings in the *Archives of Internal Medicine* (January, 1958). A recent annotation by Dr. White in this Journal, and a recent acrimonious controversy between two cardiologists in the *Journal of the American Medical Association* have prompted me to write to you today—all the more so because my observations pertain to a slightly different region of Africa, as well as to a slightly different aspect of the problems.

To begin with, I found among the natives of South Africa the same rarity of coronary atheromatosis as others have found and described (especially Bronte Stuart, G. A. Elliott, etc.). However, what is frequently overlooked in this connection is that, although coronary disease is rare among the Bantu, cerebral and renal as well as limb arteriosclerosis is very common among these people, and is quite often fatal. Thus, a unitarian, "monistic" etiological concept of atheromatosis cannot be defended—unless one accepts the highly ingenious, but so far unproved, explanation offered by Elliott (in litt.) that "the heart as an organ which is functioning physically day in and day out, year in year out, has much stronger physical stresses than the other parts of the body mentioned."

But perhaps still more interesting is the observation that I made in Ethiopia (a country which seldom figures in connection with these problems, for it is rarely visited by our physicians), in Kenya, and in Uganda, viz., that even those tribes which are quite carnivorous, e.g., the Masai, are quite immune to coronary arteriosclerosis. Now, because of my affection for the noblest, bravest, and (in my opinion) nicest people in Africa, the Masai, I visited them twice, and I could confirm the generally held belief that these epigoni of the "really great Africans" eat only meat and drink only blood and milk, and yet they do not suffer from coronary disease. One of Africa's greatest internists told me that "this is due to the fact that they walk very much." Well, in Uganda, my friend Professor Davies, certainly one of Africa's greatest pathologists, was kind enough to show me dozens of hearts (necropsy specimens) afflicted with endomyocardial fibrosis (that he so splendidly described). However, coronary thrombosis is "extremely rare among the natives . . . When seen, it . . . occurs in hard workers. Of the only two cases I have seen, one cycled 15 miles a day to market his vegetables." (in litt.)

As the reader can readily see, coronary thrombosis is rare among the Africans, both among the non-protein-eating and among the strictly fat-and-meat-eating ethnic groups, as also among the intermediate groups (Abyssinians). Incidentally, in Ethiopia, where I visited several places, the answer was everywhere the same: the "whites" have it, the "natives" do not have it, i.e., coronary disease. Now, as for the work, according to one source, hard work protects from it, whereas according to another source, hard work predisposes to it. Thus, plus ça change, plus c'est la même chose.

Perhaps I should add a remark made by Professor Davies in this connection: Fat does not CAUSE atheroma, it aggravates it. Incidentally, nonfat atheroma is apparently not rare in Africans. (Several of the foregoing remarks by Professor Davies are embodied in a paper of his in the journal *Laboratory Investigation*. However, he was kind enough to give me his findings "ahead of time.")

I hope that these few lines will help to confuse your readers as they keep me confused. But "ex tenebris lux."

Mardoqueo I. Salomon, M.D.,
F.C.C.P., F.A.C.C.

Department of Medicine
University Hospital
Edmonton, Alberta
March 15, 1961

To the Editor:

We have read the annotation "The Blight of Medical Science" by Hans H. Hecht (*American Heart Journal* 61:282, 1961) with considerable interest, understanding, and sympathy. While perhaps not in complete agreement with the proposals, we feel that a short annotation by such an acknowledged medical thinker is timely and well worthy of publication.

We have awakened from our philosophic reverie by the annotation by Dr. Mendlowitz which followed. While purporting to describe the "Bruit de Roger," the annotation concerns itself with hemodynamically significant ventricular septal defects, and a good deal of the space is devoted to information on pulmonary stenosis and atrial septal defect. The concluding sentence—"Today these clinical surmises can be confirmed or denied by the catheter and in

the operating room"—implies that clinical evaluation of patients with heart disease has remained stationary since Roger's time. Much has been written in the past few years on clinical diagnosis in heart disease by experts in this field—pointing out the accuracy with which diagnosis can be made with eyes, hands, and stethoscope. We believe that the catheter and the operating room have provided the stimulus making such clinical advances possible; that more accurate knowledge concerning auscultation has accumulated in the past 15 years than in the preceding half century; and finally that a realistic appreciation of the information to be gained by clinical examination should have been included in this annotation.

Dr. Hans Hecht deplores the volume of scientific literary effusion in which we are all being swamped. The implication is clearly that far too much is published which does not merit publication. We would agree with many of his sentiments and suggest—in retrospect—that the annotation on the "Bruit de Roger" could well have been omitted without detracting from the value of the *American Heart Journal.*

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M.R.C.P., F.R.C.P.(C)
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New York 29, N. Y.
March 30, 1961

To the Editor:

An annotation is meant to be provocative rather than provoking but in this instance it has apparently been both. It also does not necessarily incorporate a review of the literature, and if some recent efforts of the writers of this letter or of papers to which they refer have not been mentioned, I do not think that an apology is necessary.

It is always popular to praise the accuracy of the hands, eyes, ears, and stethoscope because these members and that instrument are usually available to all physicians. It therefore fortifies the ego of the clinician to decry gadgetry except as it confirms clinical experience or refines clinical interpretation. Nothing that I wrote, however, in my opinion, impugns the primacy of clinical medicine or implies that efforts should not be made to improve the interpretation of clinical auscultation.

I merely contend that when confronted with a systolic murmur loudest in the left parasternal region in the third intercostal space, it is not always possible to be certain of the underlying congenital lesion by auscultation. At least this has been in accord with my clinical experience, despite efforts to improve my acumen from reading of the experience of others, including that of my Canadian colleagues. Surely they do not propose subjecting such a patient to surgical intervention on the basis of auscultatory and routine clinical findings alone.

There is another aspect of this letter which, I believe, requires some comment. The writers criticize the Editor of the *American Heart Journal,* which is their privilege, for accepting my annotation, but soften the blow by praising that of Dr. Hecht, an "acknowledged medical thinker." The contrast thus implies that I am neither "acknowledged" or a "thinker." I presume that they would not go so far as to deny the "medical." This, however, does not disturb me very much because it occurs to me that the lack of acknowledgment is largely on the part of the writers. I agree with them, however, in their estimate of Dr. Hecht.

I cannot, however, agree with what Dr. Hecht says in his annotation and therefore must also disagree with the writers on this count. It seems to me that as the volume of scientific effort grows, the medical literature must perforce become larger. I would like to see more rather than fewer original papers published. The great advances in medicine are always a joint effort and not an extension of some individual ego. I prefer fresh original work to the warmed over potpourri of the review. How, for example, would Dr. Hecht react if his, to me, delightful and thought-provoking paper on "Brisket Disease" were ignored by some reviewer who perhaps considered it of little clinical significance or, worse, disagreed with the conclusions.

There was a time when a physician could "keep abreast" of all the medical literature. Today he can hardly do this in cardiology, and the time will come, if it has not already come, when at least I will not be able to keep up with the advances in auscultation. I wish the writers of this letter better luck but do not think that this end warrants suppression of medical literature and therefore to some extent of scientific effort.

Milton Mendlowitz, M.D.,
F.A.C.P., F.A.C.C.P.

Book reviews

NIERENKRANKHEITEN. By Prof. Dr. François Reubi, Professor für innere Medizin, und Direktor der Medizinischen Universitäts-Poliklinik, Bern, Switzerland. Bern and Stuttgart, 1960, Verlag Hans Huber, 758 pages, 173 illustrations. Price: DM. 88.

This is a new monograph on diseases of the kidney, and although published first in German, it was written in French and then translated by two of the author's colleagues. For English-speaking readers the resulting text is probably easier to read than most books in the German language.

In the first 125 pages there are brief accounts of anatomy and physiology, and a good presentation of renal function tests, including the estimation of renal blood flow and glomerular filtration rate. These latter are evidently used more frequently by Reubi in daily hospital practice than by most, and receive proportionately greater emphasis throughout the sections of the monograph dealing with individual diseases. Whatever one may think about their routine use, it is good to have a summary of what can and cannot be expected of clearance determinations by an exponent who has applied them extensively. The superiority of the 15-minute collection in the performance of the P.S.P. test is recognized, but the directions to have the patient empty the bladder before the injection of dye continues to be given, in spite of the advantage which a large specimen affords in reducing the error due to residual urine.

The major part of the book is divided into sections dealing with: (1) glomerular diseases; (2) tubular and interstitial diseases, including pyelonephritis and the shock kidney; (3) vascular nephropathies; (4) functional disturbances. Two final chapters are concerned with the treatment of acute and chronic renal insufficiency. The classification used is similar to that of Allen. Each disease is discussed systematically, with frequent emphasis on pathophysiology, and significant points are often illustrated with pertinent case histories. There are also numerous illustrations of renal biopsies, which, unfortunately, are often not reproduced well enough to be truly helpful. Useful space for other diseases is happily preserved by keeping the discussion of essential hypertension within reasonable limits, occupying only 77 pages.

In his discussion of pyelonephritis, Reubi does not mention quantitative bacteriology of the urine nor (because of its simplicity, a greater omission) the importance of a stained smear of freshly collected urine. He has recognized the occurrence of splenomegaly in pyelonephritis but was unaware of its having been found earlier by Tracy B. Mallory. The important contribution of Kincaide-Smith, and associates, on the pathology of malignant hypertension was apparently overlooked.

Professor Reubi's book is quite comprehensive and it is difficult to recall any significant disorders which have not been adequately discussed. Its wide scope and predominantly clinical emphasis combine to give it a character which is not matched by any recent monograph in the English language, and it is recommended to physicians who read German.

CLINICAL CARDIOPULMONARY PHYSIOLOGY. Edited by Burgess L. Gordon, M.D. (92 contributors). Sponsored by the American College of Chest Physicians. Second edition, New York, 1960, Grune & Stratton, Inc., 1,001 pages, 728 illustrations. Price $28.50.

A comprehensive presentation of the vast field of cardiopulmonary physiology would be an enormous task. An attempt to accomplish that in this volume has resulted in a collection of 1,001 pages contributed to by 92 different authors, many outstanding authorities in their field.

The material is presented in 63 chapters divided into 12 large sections. These sections are as follows: I. Cardiac Physiology—General Considerations; II. Evaluation of Cardiovascular Physiology; III. Physiologic Aspects of Cardiovascular Diseases; IV. Associated Functions of the Heart and Lungs; V. Pulmonary Physiology—General Considerations; VI. Evaluation of Pulmonary Physiology; VII. Restrictive Diseases of the Chest; VIII. Obstructive Diseases of the Chest; IX. Chest Diseases With Both Obstructive and Restrictive Components; X. Physiologic Therapy of Pulmonary Diseases; XI. Diseases of the Mediastinum; XII. The Relation of Special Environmental Influences to Cardiopulmonary Physiology. In the volume, 378 pages are devoted to cardiovascular structure, physiology and disease, 80 pages to associated functions of the heart and lungs, 439 pages to pulmonary structure, physiology and disease, 19 pages to mediastinal disease, and 66 pages to special environmental influences on cardiopulmonary physiology.

This type of volume, by many authors covering many topics, is extremely difficult to review critically. To point out several minor errors, controversies, or inconsistencies is hardly worth while. Only general comments and a few illustrative points can be given. The presence of a few excellent and outstanding contributions does not justify praise for the whole work. Also a few poor sections do not detract heavily from the over-all basic value of the volume. It is not feasible to comment on each of the 63 chapters nor even to list them by titles in this review.

To decide exactly to what segment of readers the volume is directed is difficult. Certainly, however, there is something of value here for all members of the medical and allied fields. For the general practitioner, much could be gained, but the coverage is possibly too time-consuming. For the cardiologist, inadequate space is given to certain areas, which makes coverage in his specialty far from comprehensive. He should gain much, however, from the sections which deal with pulmonary disease and physiology. Contrariwise, the

chest physician should find the sections on cardiovascular physiology and disease quite useful. Perhaps the greatest over-all values could be derived for the physiologically oriented general internist and thoracic surgeon.

From the cardiological view, a few specific points bear mention. One might expect to find in this volume more thorough coverage of basic principles of electrocardiography and vectorcardiography. Only a total of 16 pages is devoted to both of these subjects. This seems disproportionate in comparison to 26 pages on phonocardiography and 14 pages on cinecardioangiography. In a volume such as this, one might expect to find emphasis on pathophysiologic mechanisms, yet explanations of such phenomena as pulsus paradoxus, pulsus alternans, gallop rhythms, auscultatory gaps, etc., are inadequate. Only 7 pages are allotted to a chapter on hypertension, and over half of this deals with therapy. A chapter is devoted to resuscitation, yet little mention is made of closed-chest resuscitative procedures. One chapter deals with peripheral vascular physiology, but this is incomplete and contains little information on peripheral vascular disease. This reviewer feels that the volume would be much more useful if subjects not adequately covered (e.g., therapy of many disease states) had been omitted entirely, and the resulting space had been allotted to an expanded coverage of pathophysiologic mechanisms.

In general, each of the chapters presented is supported by key references to the literature. This is a valuable asset and as such helps support this volume as a reference work. As a reference work, however, a gross deficiency lies in the index, in which the listings to specific items covered in the text are somewhat inadequate.

In summary, regardless of the foregoing criticisms, this is a valuable work. Although occasionally incomplete in depth, it is vast in scope and it serves as a convenient review of this major field of medicine. Some of the contributions are truly outstanding for the space allotted. In general, the volume is clearly written. The paper, printing, and illustrations are of excellent quality.

FUNDAMENTALS OF CHEST ROENTGENOLOGY. By Benjamin Felson, M.D., Professor and Director, Department of Radiology, University of Cincinnati College of Medicine, Cincinnati, Ohio; Director, Departments of Radiology, Cincinnati General, Children's, Daniel Drake, Dunham, Christian R. Holmes, and Longview Hospitals; Special Consultant, U.S.P.H.S.; and Consultant to the Dayton and Cincinnati Veterans Administration Hospitals. Philadelphia, 1960, W. B. Saunders Company, 301 pages, 450 illustrations on 238 figures. Price $10.

This work expresses the knowledge and personality of an outstanding radiologist who has made important contributions to the roentgenology of the chest. His observations have been published over the years in various journals devoted to x-rays and the chest. In this volume many of them are collected and a systematic approach to the roentgen examination of the chest is outlined. No attempt is made to describe all of the diseases of the chest or all of the thoracic aspects of systemic diseases since this has been successfully accomplished in other textbooks. Instead, after dealing with the essentials of fluoroscopy and illustrating the use of the various projections and special methods in chest roentgenography, the author goes on to discuss the interpretation of chest x-ray films in terms of the anatomic elements seen on the films. He considers separately: the lobes, the segments, the hili, vessels and lymph nodes, the pleura, the extrapleural space and diaphragm. He gives special attention to the localization of intrathoracic lesions, emphasizing the silhouette sign which he has popularized and the air bronchogram. A number of other special chest x-ray signs are presented in a later chapter.

This book will be of great value for all those interested in the diagnosis of disease within the chest. This includes the radiologist, the specialist in pulmonary diseases, the cardiologist, the surgeon, and the general physician. The cardiologist will find the following features of special interest: the book offers a very clear statement concerning many of the pulmonary lesions associated with heart disease; the changes which occur within the lungs along the borders of the heart and the great vessels are well illustrated; an extended discussion of the appearances of the pulmonary arteries and veins and the changes in their appearance in the course of cardiac and other diseases is presented; the limits of interpretation concerning appearances of pulmonary arteries and veins are well drawn. The significance of peculiar shadows, such as the density sometimes seen behind the right heart, is explained; it is a reflection of the pleura at a point where the pulmonary veins come together.

This excellent monograph is peppered with instances of the author's well-known wit—an added dividend to this fine contribution to the understanding of intrathoracic diseases.

BLOOD FLOW IN ARTERIES. By Donald A. McDonald, M.A., D.M. (Oxon.), D.Sc. (Lond.), Reader in Physiology in the University of London at the Medical College of St. Bartholomew's Hospital, London, England. London, 1960, W. & J. MacKay & Co., Ltd.; Baltimore, William & Wilkins Co., 328 pages. Price $8.50.

This monograph contains a hydrodynamic analysis of pulsatile flow patterns in the circulation, which is viewed as a system in a steady-state of oscillation. This contrasts with the conventional study of pulsatile pressure changes and the use of the Windkessel analogy of Otto Frank. The latter approach is believed by the author to have outgrown its usefulness.

The scope and flavor of this book are indicated by the table of contents, which lists chapters dealing with the nature of flow in a liquid, characteristics of blood flow in the circulation, disturbances in blood flow due to the configura-

tion of the vascular bed, pressure-flow relationship of oscillatory flow, measurement of phasic flow velocity, pulsatile flow pattern in arteries, physical properties of the arterial wall, pulsatile flow in an elastic tube, wave reflection, design of manometers, shape of the pressure pulse wave, and the estimation of cardiac output from pressure recordings. Each topic is treated concisely and critically. The author clearly develops and supports his own points of view. Experimental limitations and difficulties as well as areas of ignorance are clearly pointed out.

This book should be most useful to the physiologist who wishes a thorough survey of this particular area. The physiologically oriented clinician may be frightened away by the plethora of mathematical formulae and by the technical nature of much of the discussion. If he gets into this work, he will find that the text is understandable and profitable. He may suspect the author of pleasurably flexing his technical muscles at times, occasionally losing sight of the topic or goal at hand. Although the author regards this approach as the most promising one for the future, there are no revelations for the physician beset by the problems of hypertension or arterial obstruction.

The style and format are in tradition expected from the best British publications on physiology. This book can be enthusiastically recommended to the audience for which it is intended—the physiologists of the present and future.

DIFFERENTIALDIAGNOSE INNERER KRANKHEITEN (Differential Diagnosis of Internal Disease). By Prof. Dr. Robert Hegglin, Professor für innere Medizin, Universität Zurich, Zurich, Switzerland; Direktor der Medizinischen, Universitäts-Poliklinik. Seventh revised edition, Stuttgart, 1960, Georg Thieme, 913 pages. Price: DM 79.50. (In the U.S.A. and Canada, Intercontinental Medical Book Corp., New York.)

In the preface to the first edition, published in 1952, Hegglin points out two items which he hopes will give special value to his book: that the pronouncement of general principles and general lines of orientation may fully compensate for the lack of knowledge in some special details, and that the methods of description may give an easier view for students and practitioners. The further six editions within seven years have shown that this target has been reached in every respect. As far as possible, the grouping of the diseases has been arranged according to pathophysiologic ideas.

The details of description are: general aspects; anemias; hemorrhagic diathesis; febrile states; headache; dyspnea; arrhythmias; electrocardiographic changes; cyanosis; thoracic pain; hypertension; hypotension; pulmonary infiltrations; hilar enlargements; enlarged lymph nodes; lymphoma; abdominal pain; diarrhea; obstipation; jaundice; splenomegaly; hematuria; proteinuria; pyuria; cylindruria; edema; pains in arms, legs, and spine; paralysis of the motor system; unconciousness; and disturbance of water and electrolyte balance as well as pH equilibration.

This book gives the best confirmation for the author's point of view that only through a total synthesis of all information gained from the study of patients is the possibility for rational medical action gained. In this capacity the study of Hegglin's Differentialdiagnose can be readily recommended to the specialist. For instance, for the cardiologist it is most exciting and worth while to read the author's ideas concerning the numerous relationships of cardiovascular diseases to diseases of other organ systems.

Before the preface to the seventh edition, the author has placed the sentence: "The secret of modern internal medicine is based on the conception and coordination of the efforts of its specialists." This difficult task has been fully realized by Hegglin. The dedication of the seventh edition to K. Jaspers as the mentor for medical unity should give an impulse to all to remember this goal.

DIE BEHANDLUNG DER ANGINA PECTORIS MIT "TERSAVID" UND ANDEREN MONOAMINOXYDASEHEMMERN (Treatment of Angina Pectoris With "Tersavid" and Other Monoamine Oxidase Inhibitors). Supplement II to Volume 37 of *Cardiologia*. Basel, 1960, S. Karger, 288 pages, 51 illustrations. Available in U.S.A. through Albert J. Phiebig, P.O. Box 352, White Plains, N.Y. Price $10.60.

The papers read at Lugano, in October, 1959, at a meeting of pharmacologists, toxicologists, and physicians to discuss the treatment of angina pectoris with "Tersavid" and other monoamine oxidase inhibitors are reported in this supplement to *Cardiologia*.

The theoretical aspects of the use of monoamine oxidase inhibitors and the clinical experiences with these agents in angina pectoris are reported. However, most of the experiments reported preliminary data, and the clinical experiences of most investigators were based on a relatively small series of patients. The point is well made that the clinical use of the so-called monoamine oxidase inhibitors has preceded adequate biochemical and pharmacologic knowledge of the actions of these agents. It is stated that the clinician has had to point the way for the basic investigations of these agents. Whether this is necessarily good remains to be seen. A second point of consideration is the lack of a substantial number of long-term experimental studies. The use of reserpine and now the use of MAO inhibitors has pointed to the need for experiments designed to study the long-term effects of drugs, at least 3 to 6 months. Often the effects seen on the second or third day in the pretreated animal are quite different from the immediate effect. This point should indicate that the pharmacologic basis for the use of these agents will require considerable investigative time.

In the section on theoretical aspects an attempt

is made to relate the biochemical and pharmacologic effects of this group of substances to their clinical action in angina pectoris. Several hypotheses concerning the action mechanism are advanced. An increase in the blood level of 5-hydroxytryptamine with a reduction in coronary resistance and augmentation of coronary flow without increased oxygen consumption in the left ventricle was reported. The levels of catecholamines in myocardial tissue were increased, and the suggestion is made that the MAO inhibitors could suppress the ischemic effects of these amines. Alterations in cardiac metabolism which indicate a reduction in the oxygen requirements or a more economical use of oxygen are suggested. Blockade of neurohumoral transmission which causes an increase in the threshold to sympathetic stimulation and a reduced pain conduction is also proposed. Possible participation of diamine oxidase inhibition was suggested. Over a year after this symposium we still lack much essential knowledge about the biochemical and pharmacologic effects of these agents. It seems sad to this investigator that the name *MAO inhibitors* has been given these agents, since they have many other effects that seem to be unrelated to this property.

The clinical aspects of the use of these agents is adequately discussed by H. I. Russek. It is pointed out that although these agents will produce symptomatic relief of the pain of angina pectoris, no improvement is seen in the ECG change with exercise in these patients. The compounds do not improve the ratio of oxygen supply to demand. The lack of improvement in the ECG changes with exercise observed by Russek was supported by Dighiero and co-workers. These two investigations comprised the largest groups of patients observed by one team of investigators. A total of 594 cases were reported by the 14-physician groups. Approximately two thirds of the patients were reported to have a reduction in the frequency and intensity of anginal pain.

Tersavid was found to be less toxic than Marsilid on a milligram for milligram basis; however, Tersavid is less effective than the prototype Marsilid. The recommended initial dose appears to be between 150 and 300 mg. per day. Maintenance dosage was about 100 mg. per day. The drug generally starts to take effect within the first week of treatment, but some cases require a greater period prior to the onset of action.

A fair review of the literature in regard to the actions of these agents at the time of the symposium is included. The book is recommended to investigators interested in these agents.

Announcements

THE ELEVENTH ANNUAL INSTRUMENT SYMPOSIUM AND RESEARCH EQUIPMENT EXHIBIT will be held at the National Institutes of Health, Bethesda, Md., Oct. 9 through Oct. 12, 1961.

Instrument Symposium. Committee on Symposium on Recent Developments in Research Methods and Instrumentation: Chairman, Dr. Julius Sendroy, Jr., Naval Medical Research Institute, Bethesda, Md.; Executive Secretary, Mr. James B. Davis, National Institutes of Health.

The primary topics for discussion on the scientific program include: (1) Applied Gas Chromatography; (2) Factors Influencing Interpretation of Spectra; (3) Electron Magnetic Resonance; (4) Thermogravimetric Analysis; (5) Electron Probe Analysis; (6) Application of Physiological Instrumentation to Clinical Problems; and (7) Optical Rotatory Dispersion.

Research Equipment Exhibit. Committee on Manufacturers' Representatives: Chairman, Mr. Louis Heiss, American Instrument Company, Inc., 8030 Georgia Ave., Silver Spring, Md.; Exhibit Manager, Mr. James B. Davis, National Institutes of Health, Phone OLiver 6-4000, Ext. 2315.

Examples of the latest types of research equipment will be exhibited by instrument manufacturers.

Sponsors are the Washington sections of: American Association of Clinical Chemists, American Chemical Society, Instrument Society of America, Society of American Bacteriologists, Society of Applied Spectroscopy, and Society for Experimental Biology and Medicine.

THE COUNCIL ON SCIENTIFIC ASSEMBLY OF THE AMERICAN MEDICAL ASSOCIATION invites physicians to submit titles and brief abstracts of scientific papers that they wish to deliver at the 1962 annual meeting of the American Medical Association, which will be held in Chicago, June 11-15, 1962. The deadline is Oct. 15, 1961.

"We would like to receive as many titles and abstracts as possible," said Council Chairman Samuel P. Newman, of Denver, "because in that way we have better selection, and this, in turn, assures a more timely and better scientific program."

The American Medical Association meeting in 1962 will be held in Chicago's new $35,000,000 exposition center on Lake Michigan, which has 300,000 square feet of exhibit space alone.

Physicians who wish to participate in the Chicago scientific program and desire information are invited to write to Dr. Charles Bramlitt, Secretary, Council on Scientific Assembly, American Medical Association, 535 North Dearborn St., Chicago 10, Ill., or to any council member.